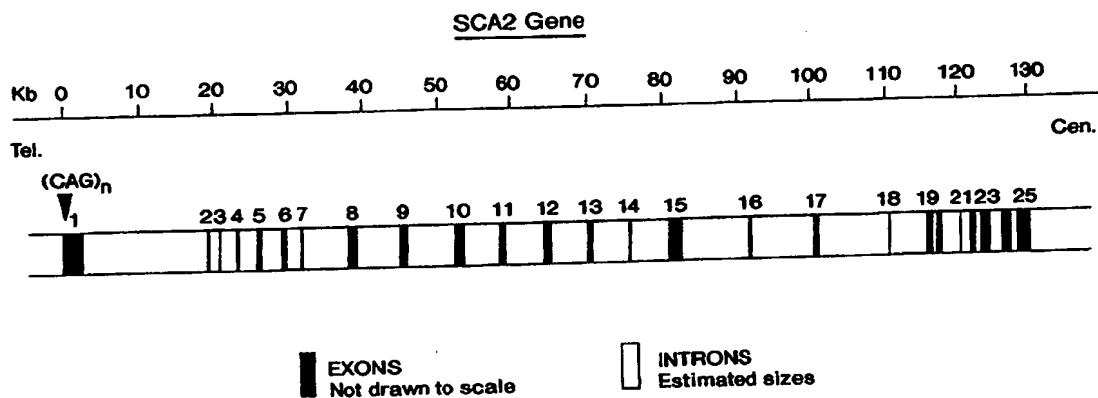




INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : C12N 15/00, 15/12, 5/10, C07K 14/47, 16/18, C12Q 1/68, G01N 33/577, A01K 67/027		A1	(11) International Publication Number: WO 97/42314
			(43) International Publication Date: 13 November 1997 (13.11.97)
(21) International Application Number: PCT/US97/07725		(74) Agents: RAMOS, Robert, T. et al.; Campbell & Flores LLP, Suite 700, 4370 La Jolla Village Drive, San Diego, CA 92122 (US).	
(22) International Filing Date: 8 May 1997 (08.05.97)			
(30) Priority Data:		(81) Designated States: CA, JP, US, European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).	
60/017,388	8 May 1996 (08.05.96) US		
60/022,207	19 July 1996 (19.07.96) US		
08/727,084	8 October 1996 (08.10.96) US		
(60) Parent Application or Grant		Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>	
(63) Related by Continuation			
US	08/727,089 (CIP)		
Filed on	8 October 1996 (08.10.96)		
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(54) Title: NUCLEIC ACID ENCODING SPINOCEREBELLAR ATAXIA-2 AND PRODUCTS RELATED THERETO



-Largest exon: exon 1, 928 bps: contains CAG repeat
 -Largest intron: intron 1 with approximately 15 Kbps
 -Smallest exon: exon 2, 37 bps

- Exon sizes:
 8<100 bps
 100 bps<12<200 bps
 200 bps< 4<400 bps
 400 bps< 1

- known intron sizes:
 intron 2 : 1.6 Kb
 intron 19: 0.3 Kb
 intron 22: 1.0 Kb
 intron 24: 1.6 Kb

(57) Abstract

The present invention provides isolated nucleic acids encoding human SCA2 protein, or fragments thereof, and isolated SCA2 proteins encoded thereby. Further provided are vectors containing invention nucleic acids, probes that hybridize thereto, host cells transformed therewith, antisense oligonucleotides thereto and compositions containing antibodies that specifically bind to invention polypeptides, as well as transgenic non-human mammals that express the invention protein. In addition, methods for diagnosing spinocerebellar Ataxia Type 2 are provided.

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NUCLEIC ACID ENCODING SPINOCEREBELLAR ATAXIA-2
AND PRODUCTS RELATED THERETO

BACKGROUND OF THE INVENTION

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Disorders of the cerebellum and its connections are a major cause of neurologic morbidity and mortality. One of the cardinal features of lesions in these pathways is ataxia or incoordination of movements and gait. Although some of the lesions have obvious etiologies such as trauma, strokes or tumors, the etiology of many ataxias has remained difficult to define and is due to metabolic deficiencies, remote effects of cancer or genetic causes. Hereditary spinocerebellar degenerations have a prevalence of 7 - 20 cases per 100,000 (Filla et al., *J. of Neurology* 239(6):351-353 (1992); Polo et al., *Brain* 114 (pt2):855-866 (1991)) which equals the estimates for the prevalence of multiple sclerosis in the United States Based on clinical analysis and genetic inheritance patterns several forms of ataxias are now recognized. Among the genetic causes of ataxic disorders, the autosomal dominant spinocerebellar ataxias (SCAs) have been the most difficult to classify and until recently no clues to their cause existed.

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The SCAs are progressive degenerative neurological diseases of the nervous system characterized by a progressive degeneration of neurons of the cerebellar cortex. Degeneration is also seen in the deep cerebellar nuclei, brain stem, and spinal cord. Clinically, affected individuals suffer from severe ataxia and dysarthria, as well as from variable degrees of motor disturbance and neuropathy. The disease usually results in complete disability and eventually in death 10 to 30 years after onset of symptoms. The genes for SCA types 1 and 3 have been identified. Both contain CAG DNA repeats that cause the disease when expanded. However, little is known how CAG repeat expansion and consequent elongation of

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polyglutamine tracts translate into neurodegeneration. The identification of the SCA2 gene would provide the opportunity to study this phenomenon in a new protein system.

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The significance of identifying ataxia genes goes beyond improved diagnosis for individuals, the possibility of prenatal/presymptomatic diagnosis or better classification of ataxias. Most of the genes associated with repeat expansions in the coding region including the genes for SCA1 and SCA3 are genes that show no homology to known genes. Thus, isolation of these genes will likely point to pathways leading to late-onset neurodegeneration that are novel and may have importance for other neurodegenerative diseases.

For example, it has been suggested that CAG expansion may result in increased transglutamination of proteins, a process that has also been implicated in Alzheimer's disease. The ataxias in particular offer the unique opportunity to study how different genes may either independently or through conjoined action in the same pathway produce relatively similar phenotypes in humans. Therefore, it may be possible to examine the interaction of these genes on age of onset and phenotype, and explain that part of phenotypic variability that is not explained by determining repeat expansion in the mutant allele. Cosmids and YACs have been the main tools for generating contig maps of chromosomal regions and the entire genome, respectively. Recently, novel cloning vectors (reviewed in Ioannou et al., Nat. Genet. 6:84-89 (1994)) have been developed that may be more stable than cosmids, while being considerable larger.

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Several systems of classification have been proposed for the SCAs based on pathological, clinical or genetic criteria. However, these attempts have been

hampered by the extreme variability of disease onset and clinical features within and between families. Among the dominant ataxias only Machado-Joseph disease (MJD) has been clinically defined as a separate disease based on the prominence of basal ganglia involvement. However, since phenotypic variability is remarkable in MJD pedigrees, the assignment of individual cases or small families to this category is difficult. Indeed, after identification of the MJD locus (SCA3) it has become apparent that families with a phenotype not typical of MJD, but resembling SCAs are linked to the same locus as SCA3 families.

The advent of genetic linkage analysis provided a novel means to approach classification of the SCAs. Since the late 70's it was recognized that some SCA pedigrees appeared to show linkage to the HLA locus on CHR6, while others did not. Later this locus, now called SCA1, was further defined using RFLP and microsatellite markers and was mapped centromeric to the HLA locus. After the establishment of flanking markers for the SCA1 gene it became rapidly apparent that many- if not the majority- of SCA families did not show linkage to the SCA1 locus. Recently, a second SCA locus was identified on CHR12 using a large pedigree of Cuban descent (Gispert et al., Nat. Genet. 4:295-299 (1993)) and in a pedigree of Southern Italian origin (Pulst et al., Nat. Genet. 5:8-10 (1993)). At the same time a third locus for Machado-Joseph disease and other pedigrees with an SCA phenotype was identified on CHR14 (Takiyama et al., Nat. Genet. 4:300-304 (1993)). Recently, SCA4 was mapped to CHR16 and SCA5 to CHR11 (Ranum et al., Nat. Genet. 8:N3:280-284 (1994)).

Two of the SCA genes have been identified, one by a positional cloning approach, the other by a cDNA based approach. The SCA1 gene was identified by screening a cosmid contig covering the region between the two flanking

markers D6S274 and D6S89 for cosmids containing CAG repeats. A CAG repeat was isolated, and shown to be expanded in affected individuals (Orr et al., *Nat. Genet.* 4:221-226 (1993); see Table 1). The number of CAG repeats are inversely correlated with the age of onset. Recently, the complete coding sequence for the SCA1 gene has been determined. The gene does not appear to be homologous to other known genes. Despite the tissue specific effects of the mutation, SCA1 transcripts are ubiquitously expressed. By RT-PCR analysis, normal and mutated transcripts are found in tissues indicating that repeat expansion does not interfere with transcription.

The SCA3 or MJD gene was identified after several CAG containing cDNA clones had been isolated from a brain cDNA library (Kawaguchi et al., *Nat. Genet.* 8:221-227 (1994)). One of these mapped to CHR 14q32.1, the region previously identified by genetic linkage analysis to contain the SCA3 gene. The CAG repeat was expanded in affected individuals, but appears to show greater meiotic stability than other CAG repeats. The SCA3 gene has no homology to other known genes or motif structures, but related sequences were identified on CHR 8q23, 14q21, and Xp22.1.

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Although not an SCA gene in the strict sense, CAG expansion in the gene causing dentatorubral-pallidoluysian atrophy (DRPLA) may also lead to degeneration of cerebellar neurons. This gene was identified by searching published brain cDNA sequences for the presence of CAG repeats. A cDNA mapped to CHR12p was found to harbor a CAG repeat which was expanded in DRPLA patients (Koide et al., *Nat. Genet.* 6:9-13 (1994); Nagafuchi et al., *Nat. Genet.* 6:14-18 (1994)). The gene which has no known homologies is ubiquitously expressed. SCA families linked to markers on CHR 12 have been described in several ethnic backgrounds.

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The largest ones are of Cuban ancestry (H pedigree), French-Canadian and Austrian ancestry (SAK and GK pedigrees, Lopes-Cendes et al., *Am. J. Hum. Genet.* 54:774-781 (1994)) and Italian descent (FS pedigree, Pulst et al., (1993)). A smaller Tunisian pedigree has been described as well (Belal et al., *Neurology* 44:1423-1426 (1994)). Although all pedigrees have cases with early onset in recent generations, a formal age of onset analysis has only been performed for the FS pedigree. This analysis indicated clear evidence of anticipation (Pulst et al., (1993)).

The phenomenon of unstable DNA repeats raises many fascinating issues. For example, in 1991, La Spada et al. identified a polymorphic CAG repeat in the androgen receptor gene on the X chromosome that was greatly expanded in individuals with spinobulbar muscular atrophy (SBMA, Kennedy syndrome). In short succession, a total of ten diseases were found to be caused by trinucleotide repeat (TNR) expansion (Table 1). Although several unifying concepts emerge from the comparison of diseases caused by TNR expansion, important differences can be recognized as well.

Common to all diseases is a highly polymorphic number of repeats on normal chromosomes. If the repeat number reaches allele sizes in between normal and disease alleles -termed premutations- the repeat becomes unstable and may expand to the size associated with the disease state. Large number repeats have the tendency to expand further, although decreases in size are occasionally seen (Bruner et al., *New Engl. J. Med.* 328:476-480 (1993); reviewed in Brook, *Nat. Genet.* 3:279-152 (1993); Mandel, *Nat. Genet.* 4:8-9 (1993)).

TABLE 1:

Characteristics of diseases caused by TNR expansion

Disease	Type of of repeat	Location of of repeat	Number of repeats in normal alleles in disease alleles	
5				
Fragile X syndrome	CGG	5' untr.	5 - 54	200 - 200
FRAXE	GCC	unknown	6 - 25	200 - 80
FRAXF	GCC	unknown	6 - 29	300 - 500
FRA16A	GCC	unknown	16 - 49	1000 - 20000
10				
Myotonic dystrophy	CTG	3' untr.	5 - 35	100 - 200
SBMA	CAG	coding	11 - 31	40 - 62
Huntington disease	CAG	coding	15 - 38	38 - 120
CA 1	CAG	coding	25 - 36	43 - 81
DRPLA	CAG	coding	7 - 26	49 - 75
15				
MJD (SCA3)	CAG	coding	13 - 36	68 - 79

TNR expansion may be a common form of human mutagenesis. Especially if expansion is not restricted to pure CAG and CCG repeats, the number of genes predisposed to expansion may be quite large. Three diseases with cerebellar degeneration, SCA1, DRPLA, and SCA3 are caused by expansion of a CAG repeat. In these diseases clear evidence of anticipation was lacking, although very early onset cases in some families had raised this question. However, as described in Pulst et al. (1993) strong evidence for anticipation was identified in the FS pedigree with SCA2. Thus, there is a need in the art to identify the location and nucleic acid structure of the SCA2 gene.

SUMMARY OF THE INVENTION

The present invention provides isolated nucleic acids encoding the human SCA2 protein and isolated proteins encoded thereby. Further provided are vectors containing invention nucleic acids, probes that hybridize thereto, host cells transformed therewith, antisense oligonucleotides thereto and compositions containing, antibodies that specifically bind to invention polypeptides and compositions containing, as well as transgenic non-human mammals that express the invention protein. In addition, methods for diagnosing

spinocerebellar Ataxia Type 2, or a predisposition thereto, are provided.

BRIEF DESCRIPTION OF THE FIGURES

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Figure 1 shows a physical map of the SCA2 region. The location of *D12S1328* centromeric and *D12S1329* telomeric of the contig are indicated. As indicated by double forward slashes, the map is not drawn to scale between *D12S1328* and *P46F2t7*, and between *B78E14t7* and *D12S1329*. YAC, PAC and BAC clones are prefixed with 'Y', 'P', and 'B' respectively. Clones positive for a specific STS by PCR analysis are indicated by vertical lines. Solid arrows indicate end-STSS from the clone under the symbol. Sizes of all clones are shown to scale. The chimeric part of YAC clone 856_h_2 (1,100 kb) is indicated by a dashed arrow. Interstitial deletions in YACs or PACs are indicated by thin lines in brackets. The extent of the deletion in YAC Y638 .e.7 is not precisely known.

Figure 2 shows the nucleic acid sequence (SEQ ID NO:1) of plasmid PL65I22B for genomic DNA encoding the expansion of the CAG repeat in individuals with SCA2. Nucleotides 1 - 499 of Figure 2 correspond to cDNA nucleotides 392 - 890 of Figure 6 (SEQ ID NO:2). The locations of primers SCA2-A and SCA2-B are indicated by arrows. The location of a predicted splice site is indicated by a vertical arrow between nucleotides 499 and 500 (also compare with Figure 6).

Figure 3 shows an analysis of the SCA2 CAG repeat by polyacrylamide electrophoresis. A common allele of 22 repeats and a less frequent allele of 23 repeats (samples 14 and 15) are seen in normal individuals. SCA2 patients with extended alleles form 37

to 52 repeats are shown. SCA2 patients derive from two pedigrees with CHR 12 linked dominant ataxia. The pedigree structures are shown at the top. Genomic DNAs were amplified with primers SCA2-A and SCA2-B and
5 separated in a 6% polyacrylamide gel. Primer SCA2-A was end-labeled. As a size standard, single stranded M13mp18 control DNA was sequenced with sequencing primer "-40" provided by USB (United States Biochem.).

10 Figure 4 shows a Scattergram indicating that CAG repeat length and age-of-onset of disease in 33 SCA2 patients are inversely correlated.

Figure 5 shows four cDNA clones as a schematic
15 of the composite SCA2 cDNA sequence. The thick line corresponds to coding sequence, the thin line to untranslated regions. The location of the CAG repeat is indicated by a hatched box. In clone S2, the repeat was not a CAG, but a CTG repeat followed by 12 bp of sequence
20 not contained in any of the other cDNA clones.

Figure 6 shows the composite cDNA sequence (SEQ ID NO:2) obtained from assembly of the partially overlapping cDNA clones shown in Figure 5. The predicted
25 SCA2 protein product (SEQ ID NO:3) is shown below the DNA sequence. The stop codon for the SCA2 cDNA is indicated by *. The locations of primers SCA2-A, SCA2-B, and SCA2-B14 are indicated by horizontal arrows. The splice site between primers SCA2-B and SCA2-B14 is indicated by a
30 vertical arrow.

Figure 7 shows a partial amino acid sequence alignment comparison of ataxin-2 protein, the ataxin-2 related protein (A2RP), and the mouse SCA2 homologue in
35 the region of strongest homology. Codon 1 corresponds to codon 155 in Figure 6 (SEQ ID NO:3).

Figure 8 shows the genomic structure of the SCA2 gene.

DETAILED DESCRIPTION OF THE INVENTION

5

The hereditary ataxias are a complex group of neurodegenerative disorders all characterized by varying abnormalities of balance attributed to dysfunction or pathology of the cerebellum and cerebellar pathways. In many of these disorders, dysfunction or structural abnormalities extend beyond the cerebellum, and may involve basal ganglia function, oculo-motor disorders and neuropathy. Among the inherited ataxias, the classification of dominant adult onset ataxias is particularly controversial with regard to nomenclature, associated findings and pathology. The dominant spinocerebellar ataxias (SCAs) represent a phenotypically heterogeneous group of disorders with a prevalence of familial cases of approximately 1 per 100,000. This group of disorders is also designated as olivo-ponto-cerebellar atrophies (OPCAs), although this term is too restrictive a pathological label.

The high phenotypic variability within single SCA pedigrees has made clinical classification of different forms of ataxia difficult. The gene causing SCA1 has been identified on CHR 6p and the SCA3 gene has been identified on CHR 14q. These diseases are caused by expansion of a CAG repeat in the coding region of the genes. However, many SCA pedigrees do not show linkage to CHR 6p or CHR 14q, confirming the presence of non-allelic heterogeneity. Subsequent genetic linkage studies have led to the identification of SCA loci on CHR12 and some families do not show linkage to either of the above three chromosomal regions.

Described in the instant specification is the construction of the BAC (Bacterial Artificial Chromosome) Shizuya et al., *Proc. Natl. Acad. Sci. USA* 89:8794-8797 (1992) contig and PAC (P1 Artificial Chromosome) of the SCA2 region and the isolation of a novel SCA2 gene from this contiguous map unit using a technique that screens for the presence of DNA trinucleotide repeats.

Sequence analysis of the DNA sequence flanking the CAG repeat revealed an open reading frame of 317 base pairs (Figure 2). A homology search of the amino acid sequence of this open reading frame (ORF) with genes registered in Genbank/EMBL and search of the TIGR database showed no homologous proteins or homologous genomic DNA sequences. Using reverse-transcribed PCR (polymerase chain reaction) with primers SCA1-A and SCA1-B, the genomic sequence containing the CAG repeat was shown to be expressed into mRNA. Subsequently, cDNA encoding human and mouse SCA2 has been isolated as described hereinafter in Examples 4 and 7, respectively.

Accordingly, the present invention provides isolated nucleic acids, which encode a novel mammalian SCA2 protein, and fragments thereof. Such nucleic acids can be obtained, for example, from human chromosome 12, specifically at the q24.1 locus, which is the site of mutation(s) that cause SCA2.

The term "nucleic acids" (also referred to as polynucleotides) encompasses RNA as well as single and double-stranded DNA and cDNA. As used herein, the phrase "isolated" means a nucleic acid that is in a form that does not occur in nature. One means of isolating a nucleic acid encoding an SCA2 polypeptide is to probe a mammalian genomic library with a natural or artificially designed DNA probe using methods well known in the art. DNA probes derived from the SCA2 gene are particularly

useful for this purpose. DNA and cDNA molecules that encode SCA2 polypeptides can be used to obtain complementary genomic DNA, cDNA or RNA from human, mammalian (e.g., mouse, rat, rabbit, pig, and the like),
5 or other animal sources, or to isolate related cDNA or genomic clones by the screening of cDNA or genomic libraries, by methods described in more detail below. Examples of nucleic acids are RNA, cDNA, or isolated genomic DNA encoding an SCA2 polypeptide. Such invention
10 nucleic acids may include, but are not limited to, nucleic acids having substantially the same nucleotide sequence as nucleotides 163-4098 set forth in SEQ ID NO:2 (Figure 6), or at least nucleotides 163-657 or nucleotides 724-4098 of SEQ ID NO:2; or nucleotides 50-
15 3454 of SEQ ID NO:4. In a preferred embodiment, invention nucleic acids include the same nucleotide sequence as nucleotides 163-4098 of SEQ ID NO:2, or include the same nucleotide sequence as nucleotides 50-3454 of SEQ ID NO:4.

20

As employed herein, the phrase "substantially the same nucleotide sequence" refers to DNA having sufficient homology to the reference polynucleotide, such that it will hybridize to the reference nucleotide under
25 typical moderate stringency conditions. In one embodiment, nucleic acid molecules having substantially the same nucleotide sequence as the reference nucleotide sequence encodes substantially the same amino acid sequence as that of either SEQ ID NO:3, or SEQ ID NO:5.
30 In another embodiment, DNA having "substantially the same nucleotide sequence" as the reference nucleotide sequence has at least 60% homology with respect to the reference nucleotide sequence. DNA having at least 70%, more preferably 80%, yet more preferably 90%, homology to the
35 reference nucleotide sequence is preferred.

This invention also encompasses nucleic acids which differ from the nucleic acids shown in SEQ ID NO:1, SEQ ID NO:2, or SEQ ID NO:4, but which have the same phenotype. Phenotypically similar nucleic acids are also referred to as "functionally equivalent nucleic acids". As used herein, the phrase "functionally equivalent nucleic acids" encompasses nucleic acids characterized by slight and non-consequential sequence variations that will function in substantially the same manner to produce the same protein product(s) as the nucleic acids disclosed herein. In particular, functionally equivalent nucleic acids encode polypeptides that are the same as those disclosed herein or that have conservative amino acid variations. For example, conservative variations include substitution of a non-polar residue with another non-polar residue, or substitution of a charged residue with a similarly charged residue. These variations include those recognized by skilled artisans as those that do not substantially alter the tertiary structure of the protein.

Further provided are nucleic acids encoding SCA2 polypeptides that, by virtue of the degeneracy of the genetic code, do not necessarily hybridize to the invention nucleic acids under specified hybridization conditions. Preferred nucleic acids encoding the invention polypeptide are comprised of nucleotides that encode substantially the same amino acid sequence set forth in SEQ ID NO:3 (Figure 6), or SEQ ID NO:5.

As employed herein, the term "substantially the same amino acid sequence" refers to amino acid sequences having at least about 70% identity with respect to the reference amino acid sequence, and retaining comparable functional and biological properties characteristic of the protein defined by the reference amino acid sequence. Preferably, proteins having "substantially the same amino

acid sequence" will have at least about 80%, more preferably 90% amino acid identity with respect to the reference amino acid sequence (SEQ ID NO:3 or SEQ ID NO:5); with greater than about 95% amino acid sequence identity being especially preferred.

Alternatively, preferred nucleic acids encoding the invention polypeptide(s) hybridize under moderately stringent, preferably high stringency, conditions to substantially the entire sequence, or substantial portions (i.e., typically at least 15-30 nucleotides) of the nucleic acid sequence set forth in SEQ ID NO:1, SEQ ID NO:2 (Figure 6) or SEQ ID NO:4.

Stringency of hybridization, as used herein, refers to conditions under which polynucleotide hybrids are stable. As known to those of skill in the art, the stability of hybrids is a function of sodium ion concentration and temperature (See, for example, Sambrook et al., *Molecular Cloning: A Laboratory Manual* 2d Ed. (Cold Spring Harbor Laboratory, (1989); incorporated herein by reference). Stringency levels used to hybridize a given probe with target-DNA can be readily varied by those of skill in the art.

As used herein, the phrase "moderately stringent" hybridization refers to conditions that permit target-DNA to bind a complementary nucleic acid that has about 60%, preferably about 75%, more preferably about 85%, homology (i.e., identity) to the target DNA; with greater than about 90% homology to target-DNA being especially preferred. Preferably, moderately stringent conditions are conditions equivalent to hybridization in 50% formamide, 5X Denhart's solution, 5X SSPE, 0.2% SDS at 42°C, followed by washing in 0.2X SSPE, 0.2% SDS, at 65°C. Denhart's solution and SSPE (see, e.g., Sambrook et al., *Molecular Cloning, A Laboratory Manual*, Cold Spring

Harbor Laboratory Press, (1989)) are well known to those of skill in the art as are other suitable hybridization buffers.

5 Also provided are isolated SCA2 peptides, polypeptides(s) and/or protein(s), or fragments thereof, encoded by the invention nucleic acids.

10 As used herein, the term "isolated" means a protein molecule free of cellular components and/or contaminants normally associated with a native *in vivo* environment. Invention polypeptides and/or proteins include any isolated natural occurring allelic variant, as well as recombinant forms thereof. The SCA2
15 polypeptides can be isolated using various methods well known to a person of skill in the art. The methods available for the isolation and purification of invention proteins include, precipitation, gel filtration, ion-exchange, reverse-phase and affinity chromatography.
20 Other well-known methods are described in Deutscher et al., *Guide to Protein Purification: Methods in Enzymology* Vol. 182, (Academic Press, (1990)), which is incorporated herein by reference. Alternatively, the isolated polypeptides of the present invention can be
25 obtained using well-known recombinant methods as described, for example, in Sambrook et al., *supra.*, 1989).

30 An example of the means for preparing the invention polypeptide(s) is to express nucleic acids encoding the SCA2 in a suitable host cell, such as a bacterial cell, a yeast cell, an amphibian cell (i.e., oocyte), or a mammalian cell, using methods well known in the art, and recovering the expressed polypeptide, again
35 using well-known methods. Invention polypeptides can be isolated directly from cells that have been transformed

with expression vectors, described below in more detail. The invention polypeptide, biologically active fragments, and functional equivalents thereof can also be produced by chemical synthesis. For example, synthetic

5 polypeptides can be produced using Applied Biosystems, Inc. Model 430A or 431A automatic peptide synthesizer (Foster City, CA) employing the chemistry provided by the manufacturer.

10 As used herein, the phrase "SCA2" refers to substantially pure native SCA2 protein, or recombinantly expressed/produced (i.e., isolated or substantially pure) proteins, including variants thereof encoded by mRNA generated by alternative splicing of a primary
15 transcript, and further including fragments thereof which retain native biological activity. Preferred invention polypeptides are those that contain substantially the same amino acid sequence set forth in SEQ ID NO:3 (Figure 6), or at least amino acids 1-165 or amino acids 188-1312
20 of SEQ ID NO:3, or include substantially the same amino acid sequence set forth in SEQ ID NO:5. As used herein, the phrase "functional polypeptide" means a SCA2 that can produce an anti-SCA2 antibody that binds to the native SCA2 protein or to the amino acid sequence set forth in
25 SEQ ID NO:3 (Figure 6), or SEQ ID NO:5. In a preferred embodiment, invention polypeptides include the same amino acid sequence as set forth in SEQ ID NO:3 or SEQ ID NO:5.

Modification of the invention nucleic acids,
30 polypeptides or proteins with the following phrases: "recombinantly expressed/produced", "isolated", or "substantially pure", encompasses nucleic acids, peptides, polypeptides or proteins that have been produced in such form by the hand of man, and are thus
35 separated from their native *in vivo* cellular environment.

As a result of this human intervention, the recombinant nucleic acids, polypeptides and proteins of the invention

are useful in ways that the corresponding naturally occurring molecules are not, such as identification of selective drugs or compounds.

5 Sequences having "substantially the same sequence" homology are intended to refer to nucleotide sequences that share at least about 75%, preferably about 80%, yet more preferably about 90% identity with
10 invention nucleic acids; and amino acid sequences that typically share at least about 75%, preferably about 85%, yet more preferably about 95% amino acid identity with
15 invention polypeptides. It is recognized, however, that polypeptides or nucleic acids containing less than the above-described levels of homology arising as splice
15 variants or that are modified by conservative amino acid substitutions, or by substitution of degenerate codons are also encompassed within the scope of the present invention.

20 The present invention provides the isolated polynucleotide encoding SCA2 operatively linked to a promoter of RNA transcription, as well as other regulatory sequences. As used herein, the phrase
25 "operatively linked" refers to the functional relationship of the polynucleotide with regulatory and effector sequences of nucleotides, such as promoters, enhancers, transcriptional and translational stop sites, and other signal sequences. For example, operative
30 linkage of a polynucleotide to a promoter refers to the physical and functional relationship between the polynucleotide and the promoter such that transcription of DNA is initiated from the promoter by an RNA
35 polymerase that specifically recognizes and binds to the promoter, and wherein the promoter directs the transcription of RNA from the polynucleotide.

Promoter regions include specific sequences that are sufficient for RNA polymerase recognition, binding and transcription initiation. Additionally, promoter regions include sequences that modulate the recognition, binding and transcription initiation activity of RNA polymerase. Such sequences may be *cis* acting or may be responsive to *trans* acting factors. Depending upon the nature of the regulation, promoters may be constitutive or regulated. Examples of promoters are SP6, T4, T7, SV40 early promoter, cytomegalovirus (CMV) promoter, mouse mammary tumor virus (MMTV) steroid-inducible promoter, Moloney murine leukemia virus (MMLV) promoter, and the like.

Vectors that contain both a promoter and a cloning site into which a polynucleotide can be operatively linked are well known in the art. Such vectors are capable of transcribing RNA *in vitro* or *in vivo*, and are commercially available from sources such as Stratagene (La Jolla, CA) and Promega Biotech (Madison, WI). In order to optimize expression and/or *in vitro* transcription, it may be necessary to remove, add or alter 5' and/or 3' untranslated portions of the clones to eliminate extra, potential inappropriate alternative translation initiation codons or other sequences that may interfere with or reduce expression, either at the level of transcription or translation. Alternatively, consensus ribosome binding sites can be inserted immediately 5' of the start codon to enhance expression. (See, for example, Kozak, *J. Biol. Chem.* 266:19867 (1991)). Similarly, alternative codons, encoding the same amino acid, can be substituted for coding sequences of the SCA2 polypeptide in order to enhance transcription (e.g., the codon preference of the host cell can be adopted, the presence of G-C rich domains can be reduced, and the like).

Also provided are vectors comprising invention nucleic acids. Examples of vectors are viruses, such as baculoviruses and retroviruses, bacteriophages, cosmids, plasmids and other recombination vehicles typically used in the art. Polynucleotides are inserted into vector genomes using methods well known in the art. For example, insert and vector DNA can be contacted, under suitable conditions, with a restriction enzyme to create complementary ends on each molecule that can pair with each other and be joined together with a ligase. Alternatively, synthetic nucleic acid linkers can be ligated to the termini of restricted polynucleotide. These synthetic linkers contain nucleic acid sequences that correspond to a particular restriction site in the vector DNA.

Additionally, an oligonucleotide containing a termination codon and an appropriate restriction site can be ligated for insertion into a vector containing, for example, some or all of the following: a selectable marker gene, such as the neomycin gene for selection of stable or transient transfectants in mammalian cells; enhancer/promoter sequences from the immediate early gene of human CMV for high levels of transcription; transcription termination and RNA processing signals from SV40 for mRNA stability; SV40 polyoma origins of replication and ColE1 for proper episomal replication; versatile multiple cloning sites; and T7 and SP6 RNA promoters for *in vitro* transcription of sense and antisense RNA. Other means are well known and available in the art.

Further provided are vectors comprising nucleic acids encoding SCA2 polypeptides, adapted for expression in a bacterial cell, a yeast cell, an amphibian cell (i.e., oocyte), a mammalian cell and other animal cells. The vectors additionally comprise the regulatory elements

necessary for expression of the nucleic acid in the bacterial, yeast, amphibian, mammalian or animal cells so located relative to the nucleic acid encoding SCA2 polypeptide as to permit expression thereof.

5 As used herein, "expression" refers to the process by which nucleic acids are transcribed into mRNA and translated into peptides, polypeptides, or proteins. If the nucleic acid is derived from genomic DNA, expression may include splicing of the mRNA, if an appropriate eucaryotic host is selected. Regulatory elements required for expression include promoter sequences to bind RNA polymerase and transcription initiation sequences for ribosome binding. For example, 10 a bacterial expression vector includes a promoter such as the lac promoter and for transcription initiation the Shine-Dalgarno sequence and the start codon AUG (Sambrook et al. *supra*). Similarly, a eucaryotic expression vector includes a heterologous or homologous promoter for RNA polymerase II, a downstream polyadenylation signal, the 20 start codon AUG, and a termination codon for detachment of the ribosome. Such vectors can be obtained commercially or assembled by the sequences described in methods well known in the art, for example, the methods described above for constructing vectors in general. 25 Expression vectors are useful to produce cells that express the invention polypeptide.

The present invention provides transformed host 30 cells that recombinantly express SCA2 polypeptides. An example of a transformed host cell is a mammalian cell comprising a plasmid adapted for expression in a mammalian cell. The plasmid contains nucleic acid encoding an SCA2 polypeptide and the regulatory elements 35 necessary for expression of invention proteins. Various mammalian cells may be utilized as hosts, including, for example, mouse fibroblast cell NIH3T3, CHO cells, HeLa

cells, Ltk- cells, etc. Expression plasmids such as those described *supra* can be used to transfect mammalian cells by methods well known in the art such as, for example, calcium phosphate precipitation, DEAE-dextran, electroporation, microinjection or lipofection.

The present invention provides nucleic acid probes comprising nucleotide sequences capable of specifically hybridizing with sequences included within nucleic acids encoding SCA2 polypeptides, for example, a coding sequence included within the nucleotide sequence shown in SEQ ID NO:2 (Figure 6), or SEQ ID NO:4. In a preferred embodiment, the probe is derived from the nucleic acid sequence set forth in SEQ ID NO:2, or at least nucleotides 163-657 or nucleotides 724-4098 of SEQ ID NO:2; or SEQ ID NO:4. Preferred regions from which to construct probes include 5' and/or 3' coding sequences, sequences within the ORF, and the like. Full-length or fragments of cDNA clones encoding SCA2 can also be used as probes for the detection and isolation of related genes. As used herein, an invention "probe" or invention oligonucleotide is a single-stranded DNA or RNA that has a sequence of nucleotides that includes at least about 15 contiguous bases up to the full length coding region of SEQ ID NO:2 or SEQ ID NO:4. Preferably an invention probe is at least about 30 contiguous bases, more preferably at least about 50, yet more preferably at least about 100, with about 300 contiguous bases up to the full length coding region of SEQ ID NO:2 and SEQ ID NO:4 being especially preferred. When fragments are used as probes, preferably the cDNA sequences will be from the carboxyl end-encoding portion of the cDNA, and most preferably will include predicted transmembrane domain-encoding portions of the cDNA sequence. Transmembrane domain regions can be predicted based on hydropathy analysis of the deduced amino acid sequence using, for

example, the method of Kyte and Doolittle, *J. Mol. Biol.* 157:105 (1982).

As used herein, the phrase "specifically hybridizing" encompasses the ability of a polynucleotide to recognize a sequence of nucleic acids that are complementary thereto and to form double-helical segments via hydrogen bonding between complementary base pairs. Nucleic acid probe technology is well known to those skilled in the art who will readily appreciate that such probes may vary greatly in length and may be labeled with a detectable agent, such as a radioisotope, a fluorescent dye, and the like, to facilitate detection of the probe. Invention probes are useful to detect the presence of nucleic acids encoding the SCA2 polypeptide. For example, the probes can be used for *in situ* hybridizations in order to locate biological tissues in which the invention gene is expressed. Additionally, synthesized oligonucleotides complementary to the nucleic acids of a nucleotide sequence encoding SCA2 polypeptide are useful as probes for detecting the invention genes, their associated mRNA, or for the isolation of related genes using homology screening of genomic or cDNA libraries, or by using amplification techniques well known to one of skill in the art.

Also provided are antisense oligonucleotides having a sequence capable of binding specifically with any portion of an mRNA that encodes SCA2 polypeptides so as to prevent or inhibit translation of the mRNA. The antisense oligonucleotide may have a sequence capable of binding specifically with any portion of the sequence of the cDNA encoding SCA2 polypeptides. As used herein, the phrase "binding specifically" encompasses the ability of a nucleic acid sequence to recognize a complementary nucleic acid sequence and to form double-helical segments therewith via the formation of hydrogen bonds between the

complementary base pairs. An example of an antisense oligonucleotide is an antisense oligonucleotide comprising chemical analogs of nucleotides.

5 Compositions comprising an amount of the antisense oligonucleotide, described above, effective to reduce expression of SCA2 polypeptides by passing through a cell membrane and binding specifically with mRNA encoding SCA2 polypeptides so as to prevent translation
10 and an acceptable hydrophobic carrier capable of passing through a cell membrane are also provided herein. The acceptable hydrophobic carrier capable of passing through cell membranes may also comprise a structure which binds to a receptor specific for a selected cell type and is
15 thereby taken up by cells of the selected cell type. The structure may be part of a protein known to bind to a cell-type specific receptor.

Antisense oligonucleotide compositions are
20 useful to inhibit translation of mRNA encoding invention polypeptides. Synthetic oligonucleotides, or other antisense chemical structures are designed to bind to mRNA encoding SCA2 polypeptides and inhibit translation of mRNA and are useful as compositions to inhibit
25 expression of SCA2 associated genes in a tissue sample or in a subject.

In accordance with another embodiment of the invention, kits for detecting mutations and aneuploidies
30 in chromosome 12 at locus q24.1 comprising at least one invention probe or antisense nucleotide.

The present invention provides means to modulate levels of expression of SCA2 polypeptides by
35 employing synthetic antisense oligonucleotide compositions (hereinafter SAOC) which inhibit translation of mRNA encoding these polypeptides. Synthetic

oligonucleotides, or other antisense chemical structures designed to recognize and selectively bind to mRNA, are constructed to be complementary to portions of the SCA2 coding strand or nucleotide sequences shown in SEQ ID NO:2, or SEQ ID NO:4. The SAOC is designed to be stable in the blood stream for administration to a subject by injection, or in laboratory cell culture conditions. The SAOC is designed to be capable of passing through the cell membrane in order to enter the cytoplasm of the cell by virtue of physical and chemical properties of the SAOC which render it capable of passing through cell membranes, for example, by designing small, hydrophobic SAOC chemical structures, or by virtue of specific transport systems in the cell which recognize and transport the SAOC into the cell. In addition, the SAOC can be designed for administration only to certain selected cell populations by targeting the SAOC to be recognized by specific cellular uptake mechanisms which bind and take up the SAOC only within select cell populations.

For example, the SAOC may be designed to bind to a receptor found only in a certain cell type, as discussed *supra*. The SAOC is also designed to recognize and selectively bind to target mRNA sequence, which may correspond to a sequence contained within the sequence shown in SEQ ID NO:2, or SEQ ID NO:4. The SAOC is designed to inactivate target mRNA sequence by either binding thereto and inducing degradation of the mRNA by, for example, RNase I digestion, or inhibiting translation of mRNA target sequence by interfering with the binding of translation-regulating factors or ribosomes, or inclusion of other chemical structures, such as ribozyme sequences or reactive chemical groups which either degrade or chemically modify the target mRNA. SAOCs have been shown to be capable of such properties when directed against mRNA targets (see Cohen et al., *TIPS*, 10:435

(1989) and Weintraub, *Sci. American*, January (1990), pp.40; both incorporated herein by reference).

The present invention also provides
5 compositions containing an acceptable carrier and any of
an isolated, purified SCA2 polypeptide, an active
fragment thereof, or a purified, mature protein and
active fragments thereof, alone or in combination with
each other. These polypeptides or proteins can be
10 recombinantly derived, chemically synthesized or purified
from native sources. As used herein, the term
"acceptable carrier" encompasses any of the standard
pharmaceutical carriers, such as phosphate buffered
saline solution, water and emulsions such as an oil/water
15 or water/oil emulsion, and various types of wetting
agents.

Further provided are anti-SCA2 antibodies
having specific reactivity with SCA2 polypeptides of the
20 present invention. Active fragments of antibodies are
encompassed within the definition of "antibody".
Invention antibodies can be produced by methods known in
the art using invention polypeptides, proteins or
portions thereof as antigens. For example, polyclonal
25 and monoclonal antibodies can be produced by methods well
known in the art, as described, for example, in Harlow
and Lane, *Antibodies: A Laboratory Manual* (Cold Spring
Harbor Laboratory (1988)), which is incorporated herein
by reference. Invention polypeptides can be used as
30 immunogens in generating such antibodies. Alternatively,
synthetic peptides can be prepared (using commercially
available synthesizers) and used as immunogens. Amino
acid sequences can be analyzed by methods well known in
the art to determine whether they encode hydrophobic or
35 hydrophilic domains of the corresponding polypeptide.
Altered antibodies such as chimeric, humanized, CDR-
grafted or bifunctional antibodies can also be produced

by methods well known in the art. Such antibodies can also be produced by hybridoma, chemical synthesis or recombinant methods described, for example, in Sambrook et al., *supra.*, and Harlow and Lane, *supra.* Both anti-peptide and anti-fusion protein antibodies can be used. (see, for example, Bahouth et al., *Trends Pharmacol. Sci.* 12:338 (1991); Ausubel et al., *Current Protocols in Molecular Biology* (John Wiley and Sons, NY (1989) which are incorporated herein by reference).

10

Invention antibodies also can be used to isolate invention polypeptides. Additionally the antibodies are useful for detecting the presence of invention polypeptides, as well as analysis of chromosome localization, and structural as well as functional domains. Methods for detecting the presence of SCA2 polypeptides on the surface of a cell comprise contacting the cell with an antibody that specifically binds to SCA2 polypeptides, under conditions permitting binding of the antibody to the polypeptides, detecting the presence of the antibody bound to the cell, and thereby detecting the presence of invention polypeptides on the surface of the cell. With respect to the detection of such polypeptides, the antibodies can be used for *in vitro* diagnostic or *in vivo* imaging methods.

25

Immunological procedures useful for *in vitro* detection of target SCA2 polypeptides in a sample include immunoassays that employ a detectable antibody. Such immunoassays include, for example, ELISA, Pandex microfluorimetric assay, agglutination assays, flow cytometry, serum diagnostic assays and immunohistochemical staining procedures which are well known in the art. An antibody can be made detectable by various means well known in the art. For example, a detectable marker can be directly or indirectly attached

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to the antibody. Useful markers include, for example, radionucleotides, enzymes, fluorogens, chromogens and chemiluminescent labels.

5 Further, invention antibodies can be used to modulate the activity of the SCA2 polypeptide in living animals, in humans, or in biological tissues or fluids isolated therefrom. Accordingly, compositions comprising a carrier and an amount of an antibody having specificity
10 for SCA2 polypeptides effective to block binding of naturally occurring ligands to invention polypeptides. A monoclonal antibody directed to an epitope of SCA2 polypeptide molecules present on the surface of a cell and having an amino acid sequence substantially the same
15 as an amino acid sequence for a cell surface epitope of an SCA2 polypeptide shown in SEQ ID NO:3, or SEQ ID NO:5, can be useful for this purpose.

 The present invention further provides
20 transgenic non-human mammals that are capable of expressing nucleic acids encoding SCA2 polypeptides. Also provided are transgenic non-human mammals capable of expressing nucleic acids encoding SCA2 polypeptides so mutated as to be incapable of normal activity, i.e., do
25 not express native SCA2. The present invention also provides transgenic non-human mammals having a genome comprising antisense nucleic acids complementary to nucleic acids encoding SCA2 polypeptides so placed as to be transcribed into antisense mRNA complementary to mRNA
30 encoding SCA2 polypeptides, which hybridizes thereto and, thereby, reduces the translation thereof. The nucleic acid may additionally comprise an inducible promoter and/or tissue specific regulatory elements, so that expression can be induced, or restricted to specific cell
35 types. Examples of nucleic acids are DNA or cDNA having a coding sequence substantially the same as the coding sequence shown in SEQ ID NO:2, or SEQ ID NO:4. An

example of a non-human transgenic mammal is a transgenic mouse. Examples of tissue specificity-determining elements are the metallothionein promoter and the L7 promoter.

5

Animal model systems which elucidate the physiological and behavioral roles of SCA2 polypeptides are produced by creating transgenic animals in which the expression of the SCA2 polypeptide is altered using a variety of techniques. Examples of such techniques include the insertion of normal or mutant versions of nucleic acids encoding an SCA2 polypeptide by microinjection, retroviral infection or other means well known to those skilled in the art, into appropriate fertilized embryos to produce a transgenic animal. (See, for example, Hogan et al., *Manipulating the Mouse Embryo: A Laboratory Manual* (Cold Spring Harbor Laboratory, (1986)).

20

Another technique, homologous recombination of mutant or normal versions of these genes with the native gene locus in transgenic animals, may be used to alter the regulation of expression or the structure of SCA2 polypeptides (see, Capecchi et al., *Science* 244:1288 (1989); Zimmer et al., *Nature* 338:150 (1989); which are incorporated herein by reference). Homologous recombination techniques are well known in the art. Homologous recombination replaces the native (endogenous) gene with a recombinant or mutated gene to produce an animal that cannot express native (endogenous) protein but can express, for example, a mutated protein which results in altered expression of SCA2 polypeptides.

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In contrast to homologous recombination, microinjection adds genes to the host genome, without removing host genes. Microinjection can produce a

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transgenic animal that is capable of expressing both endogenous and exogenous SCA2 protein. Inducible promoters can be linked to the coding region of nucleic acids to provide a means to regulate expression of the transgene. Tissue specific regulatory elements can be
5 linked to the coding region to permit tissue-specific expression of the transgene. Transgenic animal model systems are useful for *in vivo* screening of compounds for identification of specific ligands, i.e., agonists and
10 antagonists, which activate or inhibit protein responses.

Invention nucleic acids, oligonucleotides (including antisense), vectors containing same, transformed host cells, polypeptides and combinations
15 thereof, as well as antibodies of the present invention, can be used to screen compounds *in vitro* to determine whether a compound functions as a potential agonist or antagonist to invention polypeptides. These *in vitro* screening assays provide information regarding the
20 function and activity of invention polypeptides, which can lead to the identification and design of compounds that are capable of specific interaction with one or more types of polypeptides, peptides or proteins.

25 In accordance with still another embodiment of the present invention, there is provided a method for identifying compounds which bind to SCA2 polypeptides. The invention proteins may be employed in a competitive binding assay. Such an assay can accommodate the rapid
30 screening of a large number of compounds to determine which compounds, if any, are capable of binding to SCA2 proteins. Subsequently, more detailed assays can be carried out with those compounds found to bind, to further determine whether such compounds act as
35 modulators, agonists or antagonists of invention proteins.

In another embodiment of the invention, there is provided a bioassay for identifying compounds which modulate the activity of invention polypeptides. According to this method, invention polypeptides are
5 contacted with an "unknown" or test substance (in the presence of a reporter gene construct when antagonist activity is tested), the activity of the polypeptide is monitored subsequent to the contact with the "unknown" or test substance, and those substances which cause the
10 reporter gene construct to be expressed are identified as functional ligands for SCA2 polypeptides.

In accordance with another embodiment of the present invention, transformed host cells that
15 recombinantly express invention polypeptides can be contacted with a test compound, and the modulating effect(s) thereof can then be evaluated by comparing the SCA2-mediated response (via reporter gene expression) in the presence and absence of test compound, or by
20 comparing the response of test cells or control cells (i.e., cells that do not express SCA2 polypeptides), to the presence of the compound.

As used herein, a compound or a signal that
25 "modulates the activity" of invention polypeptides refers to a compound or a signal that alters the activity of SCA2 polypeptides so that the activity of the invention polypeptide is different in the presence of the compound or signal than in the absence of the compound or signal.
30 In particular, such compounds or signals include agonists and antagonists. An agonist encompasses a compound or a signal that activates SCA2 protein expression. Alternatively, an antagonist includes a compound or signal that interferes with SCA2 protein expression.
35 Typically, the effect of an antagonist is observed as a blocking of agonist-induced protein activation. Antagonists include competitive and non-competitive

antagonists. A competitive antagonist (or competitive blocker) interacts with or near the site specific for agonist binding. A non-competitive antagonist or blocker inactivates the function of the polypeptide by
5 interacting with a site other than the agonist interaction site.

As understood by those of skill in the art, assay methods for identifying compounds that modulate
10 SCA2 activity generally require comparison to a control. One type of a "control" is a cell or culture that is treated substantially the same as the test cell or test culture exposed to the compound, with the distinction that the "control" cell or culture is not exposed to the
15 compound. For example, in methods that use voltage clamp electrophysiological procedures, the same cell can be tested in the presence or absence of compound, by merely changing the external solution bathing the cell. Another type of "control" cell or culture may be a cell or
20 culture that is identical to the transfected cells, with the exception that the "control" cell or culture do not express native proteins. Accordingly, the response of the transfected cell to compound is compared to the response (or lack thereof) of the "control" cell or
25 culture to the same compound under the same reaction conditions.

In yet another embodiment of the present invention, the activation of SCA2 polypeptides can be
30 modulated by contacting the polypeptides with an effective amount of at least one compound identified by the above-described bioassays.

In accordance with another embodiment of the
35 present invention, there are provided methods for diagnosing spinocerebellar Ataxia Type 2, said method comprising:

detecting, in said subject, a genomic or transcribed mRNA sequence having an expanded CAG repeat at a location corresponding to between nucleotides 657 and 724 of SEQ ID NO:2 (Figure 6).

The number of CAG repeats required to indicate spinocerebellar Ataxia Type 2 is substantially above normal, preferably at least about 10-15 CAG repeats above normal, with at least 13 CAG repeats above normal being especially preferred. A normal amount of CAG repeats in the SCA2 gene (SEQ ID NO:2) has been found to be about 22, while 23 CAG repeats is occasionally observed. Thus, in a preferred diagnostic method, at least about 35 CAG repeats are detected between nucleotides 657 and 724 of SEQ ID NO:2 (Figure 6), with the detection of 37 CAG repeats being especially preferred.

Although expansion of trinucleotide repeats is now recognized as an important mutational mechanism in humans and SCA2 represents the 6th disease in which expansion of a CAG trinucleotide repeat causes disease, there are several features of the SCA2 repeat that appear to be unique. In the other five CAG expansion diseases, the CAG repeats on normal chromosomes are highly polymorphic. Multiple alleles are detected and repeat sizes on normal chromosomes range from a low of 7 repeats in DRPLA to 40 repeats in SCA3/MJD. Heterozygosity for these CAG repeats in the normal population are in the range of 0.80 and above. It has been suggested that the extended normal alleles represent founder alleles which are predisposed to expansion.

The SCA2 repeat is highly unusual, because only two alleles are observed in the normal population. A common allele with 22 repeats is found on 92% of chromosomes, a rare second allele in 8% of chromosomes.

Expansion of the SCA2 CAG repeat on disease chromosomes is relatively moderate and is in the range seen with expansions in the SBMA and Huntington's Disease (HD) genes. The lowest number of repeats causing SCA2 was 36 and the most common disease allele had 37 repeats. Disease alleles showing 36 repeats have now clearly been established for HD (Rubinsztein et al., 1996, Am. J. Hum. Genet., 59:16-22), although normal elderly individuals with 36-40 repeats exist and the most common HD alleles have >40 repeats. In contrast to SCA1, where normal and disease alleles may differ by only one repeat unit, the longest normal and the shortest SCA2 disease allele are separated by 13 repeats. Once expanded on disease chromosomes, the SCA2 repeat may undergo moderate expansions.

The SCA2 repeat is contained in a novel gene which is transcribed in several tissues including non-neuronal tissues. The gene product, ataxin-2, has a predicted molecular weight of 140 kDa which is in good agreement with the 150 kDa protein observed using a monoclonal antibody to long polyglutamine tracts. A similar pattern of nearly ubiquitous expression has been observed in the other five polyglutamine diseases. Despite the phenotypic overlap of SCA2 with SCA1 and SCA3, the SCA2 gene shows no homology to these genes.

However, ataxin-2 showed significant homologies with another protein (referred to as "A2RP"; see Figure 7). A 42 amino acid domain was identified that was 86% identical between the two proteins. The potential functional importance of this domain was underscored by the fact that it was 100% conserved in the mouse SCA2 homologue (Figure 7). Interestingly, the polyglutamine tract was not conserved in either protein. Since the pathogenesis of polyglutamine containing proteins is still poorly understood, the identification of

functionally important domains adjacent to polyglutamine tracts may provide the potential for novel strategies to analyze the function of ataxin-2. A gain of function for the mutated ataxin-2 is supported by the fact that
5 transcripts coding for mutated alleles are detected by RT-PCR.

Expansion of the SCA2 repeat appears to be a common cause of a dominant SCA phenotype in non-
10 Portuguese patients. When samples from 45 families with SCA were screened, samples from 8 independent pedigrees showed expansion of the SCA2 repeat. It has been suggested that there are features specific to SCA2, but this assessment was limited to families large enough to
15 be studied by linkage analysis. A better assessment of the range of SCA2 phenotypes is now possible due to the ability to test small families and single cases. In our patient sample, most patients had a 'typical' SCA phenotype, but some patients had been classified as
20 having an MJD phenotype and others showed a prominent dementia.

When performing direct testing for SCA2 mutations, great caution has to be exercised when
25 interpreting the presence of expanded SCA2 alleles on polyacrylamide gels. A variable number of unrelated PCR fragments may be seen that are in the size range of expanded SCA2 repeats. Although these bands lack the typical 'shadow' bands seen when di- or trinucleotide
30 repeats are amplified, they may interfere with the interpretation in some samples. It is therefore recommended to confirm the presence of an expanded allele by Southern blotting and hybridization with a (CAG)₁₀ oligonucleotide.

In yet another embodiment of the present invention, there are provided methods for diagnosing spinocerebellar Ataxia Type 2, said method comprising:

- a) contacting nucleic acid obtained from
5 a subject suspected of having SCA2 with primers that amplify at least a nucleic acid fragment of SEQ ID NO:2 containing nucleotides 658-723 of SEQ ID NO:2, under conditions suitable to form a detectable amplification product; and
- 10 b) detecting an amplification product containing substantially expanded CAG repeats above normal, whereby said detection indicates that said subject has SCA2.

15 As indicated above, substantially expanded CAG repeats have at least about 10-15 CAG repeats above normal, with at least 13 CAG repeats above normal being especially preferred. Thus, in a preferred diagnostic method, at least about 35 CAG repeats are detected
20 between nucleotides 657 and 724 of SEQ ID NO:2 (Figure 6), with the detection of 37 CAG repeats being especially preferred.

In accordance with another embodiment of the
25 present invention, there are provided diagnostic systems, preferably in kit form, comprising at least one invention nucleic acid in a suitable packaging material. In one embodiment, the diagnostic nucleic acids are derived from SEQ ID NO:2 (Figure 6), preferably derived from
30 nucleotides 163-657 and nucleotides 724-4098, with primers SCA2-A and SCA2-B being especially preferred. In another embodiment, the diagnostic nucleic acids are derived from SEQ ID NO:4. Invention diagnostic systems are useful for assaying for the presence or absence of
35 the extended CAG repeat sequence between nucleotides 657 and 724 of SEQ ID NO:2 in the SCA2 gene in either genomic

DNA or in transcribed nucleic acid (such as mRNA or cDNA) encoding SCA2.

A suitable diagnostic system includes at least one invention nucleic acid, preferably two or more invention nucleic acids, as a separately packaged chemical reagent(s) in an amount sufficient for at least one assay. Instructions for use of the packaged reagent are also typically included. Those of skill in the art can readily incorporate invention nucleic probes and/or primers into kit form in combination with appropriate buffers and solutions for the practice of the invention methods as described herein.

As employed herein, the phrase "packaging material" refers to one or more physical structures used to house the contents of the kit, such as invention nucleic acid probes or primers, and the like. The packaging material is constructed by well known methods, preferably to provide a sterile, contaminant-free environment. The packaging material has a label which indicates that the invention nucleic acids can be used for detecting a particular extended CAG repeat sequence between the region of genomic DNA corresponding to nucleotides 657 and 724 of SEQ ID NO:2 (Figure 6), thereby diagnosing the presence of, or a predisposition for, spinocerebellar ataxia type 2. In addition, the packaging material contains instructions indicating how the materials within the kit are employed both to detect a particular sequence and diagnose the presence of, or a predisposition for, spinocerebellar ataxia type 2.

The packaging materials employed herein in relation to diagnostic systems are those customarily utilized in nucleic acid-based diagnostic systems. As used herein, the term "package" refers to a solid matrix or material such as glass, plastic, paper, foil, and the

like, capable of holding within fixed limits an isolated nucleic acid, oligonucleotide, or primer of the present invention. Thus, for example, a package can be a glass vial used to contain milligram quantities of a contemplated nucleic acid, oligonucleotide or primer, or it can be a microtiter plate well to which microgram quantities of a contemplated nucleic acid probe have been operatively affixed.

"Instructions for use" typically include a tangible expression describing the reagent concentration or at least one assay method parameter, such as the relative amounts of reagent and sample to be admixed, maintenance time periods for reagent/sample admixtures, temperature, buffer conditions, and the like.

All U.S. patents and all publications mentioned herein are incorporated in their entirety by reference thereto. The invention will now be described in greater detail by reference to the following non-limiting examples.

The invention will now be described in greater detail with reference to the following non-limiting examples.

Materials and Methods

Unless otherwise stated, the present invention was performed using standard procedures, as described, for example in Maniatis et al., Molecular Cloning: A Laboratory Manual, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, New York, USA (1982); Sambrook et al., Molecular Cloning: A Laboratory Manual (2 ed.), Cold Spring Harbor Laboratory Press, Cold Spring Harbor, New York, USA (1989); Davis et al., Basic Methods in

Molecular Biology, Elsevier Science Publishing, Inc., New York, USA (1986); or *Methods in Enzymology: Guide to Molecular Cloning Techniques* Vol.152, S. L. Berger and A. R. Kimmerl Eds., Academic Press Inc., San Diego, USA (1987)).

Libraries. Yeast artificial chromosome (YAC) clones were obtained from the CEPH mega-YAC library and grown under standard conditions (Cohen et al., *Nature* 366:689-701 (1993)). P1 artificial chromosome (PAC) library construction. A 3X human PAC library, designated RPCI-1 (Ioannou et al., *Hum. Genet.* 219-220 (1994b)) was constructed as described (Ioannou et al., *Nat. Genet.* 6:84-89 (1994a)). The library was arrayed in 384 well dishes. Pools from portion of the library were screened by PCR with AFM154TC5 (D12S1333) and AFMa128yf1 (D12S1332). Subsequently, STSs generated by sequencing of clones using vector primers were used as hybridization probes to gridded colony filters of the PAC library.

YAC DNA preparation. YAC clones were grown in selective media, pelleted and resuspended in 3 ml 0.9 M sorbitol, 0.1M EDTA pH 7.5, then incubated with 100 U of lytocase (Sigma) at 37°C for 1 hour. After centrifugation for 5 minutes at 5,000 rpm pellets were resuspended in 3 ml 50 mM Tris pH 7.45, 20 mM EDTA three-tenth ml 10% SDS was added and the mixture was incubated at 65°C for 30 minutes. One ml of 5 M potassium acetate was added and tubes were left on ice for 1 hour, then centrifuged at 10,000 rpm for 10 minutes. Supernatant was precipitated in 2 volumes of ethanol and pelleted at 6,000 rpm for 15 minutes. Pellets were resuspended in TE, treated with RNase and reextracted with phenol-chloroform.

Analysis by pulsed-field gel electrophoresis.

Agarose plugs of yeast cells containing total YAC DNA were prepared (Larin and Lehrach, *Genet. Res.* 56:203-208 (1990)) and subjected to pulsed-field gel separation on 5 1% SeaKem agarose gels in 0.5X TBE using the CHEF DRII Mapper (Bio-Rad). PAC and BAC clones were sized after digestion with XbaI and NotI. Gels were blotted onto Magna NT Nylon membranes using alkaline blotting, UV 10 cross linked and baked at 80°C for two hours. Membranes were hybridized with total human DNA, washed according to standard procedures, and exposed to Kodak XAR5 film. The sizes of individual clones were determined by comparison to their relative positions with molecular weight standards.

15

Analysis by fluorescence in situ hybridization

(FISH). PAC or BAC clones were biotinylated by nicktranslation in the presence of biotin-14-dATP using the BioNick Labeling Kit (Gibco-BRL). FISH was performed 20 essentially as described (Korenberg et al., *Cytogenet Cell Genet.* 69:196-200 (1995)). Briefly, 400 ng of probe DNA was mixed with 8 ng of human Cot 1 DNA (Gibco-BRL) and 2 ug of sonicated salmon sperm DNA in order to suppress possible background produced from repetitive 25 human sequences as well as yeast sequences in the probe. The probes were denatured at 75°C, preannealed at 37°C for one hour, and applied to denatured chromosome slides prepared from normal male lymphocytes (Korenberg et al., 1995, *supra*). Post-hybridization washes were performed 30 at 40°C in 2X SSC/50% formamide followed by washes in 1X SSC at 50°C. Hybridized DNAs were detected with avidin-conjugated fluorescent isothiocyanate (Vector Laboratories). One amplification was performed by using biotinylated anti-avidin. For distinguishing chromosome 35 subbands precisely, a reverse banding technique was used, which was achieved by chromomycin A3 and distamycin A

double staining (Korenberg et al., 1995, *supra*). The color images were captured by using a Photometrics Cooled-CCD camera and BDS image analysis software (Oncor Imaging, Inc.).

5

PAC and BAC DNA preparation. Selected clones were grown overnight in LB media containing 12.5 µg/ml kanamycin for PACs and 12.5 µg/ml chloramphenicol for BACs. DNAs were prepared by the alkaline lysis method.

10 PAC DNAs were digested with NotI and subjected to pulsed-field gel electrophoresis. Sizes were determined relative to λ concatamers.

Southern blot analysis. Gel electrophoresis of

15 DNA was carried out on 0.8% agarose gels in 1x TBE. Transfer of nucleic acids to Nybond N+ nylon membrane (Amersham) was performed according to the manufacturer's instruction. Probes were labelled using RadPrime Labeling System (BRL). Hybridization was carried out at

20 42°C for 16 hours in 50% formamide, 5x SSPE, 5x Denhardt's 0.1% SDS, 100 mg/ml denatured salmon sperm DNA. The filters were washed once in 1x SSC, 0.1% SDS at room temperature for 20 minutes, and twice in 0.1x SSC, 0.1% SDS for 20 minutes at 65°C. The blots were exposed

25 onto X-ray film (Kodak, X-OMAT-AR).

Sequencing of PAC endclones. PAC clones were inoculated into 500 ml of LB/kanamycin and grown overnight. DNAs were isolated using QIAGEN columns

30 according to the vendors protocol with one additional phenol/chloroform/isoamylalcohol extraction followed by one additional chloroform/isoamylalcohol extraction. Clones were sequenced using the Gibco-BRL cycle sequencing kit with standard T7 and SP6 primers.

35

Hybridization of (CAG)₁₀ oligonucleotides.

Eighty ng of oligonucleotide were 5' end-labeled and hybridized overnight at 42°C in buffer containing 1 M NaCl, 0.05 M Tris HCl pH7, 5.5 mM EDTA, 0.1 % SDS, 1X Denhardt's solution and 200 µg/ml denatured salmon sperm DNA. Filters were washed 2 times with 2X SSC, 0.1% SDS at 55°C and exposed to Kodak X-ray film for 24 hours, and subsequently washed at 65°C, followed by additional exposure to X-ray film.

10

Regression Analysis. The data were fit using the Statistical Analysis Software (SAS) package version 3.10 using the Secant Method (Ralston et al, 1978, Technometrics, 20:7-14). The regression equation was $y = A \cdot \exp(-ax)$, where y gives the age of onset and x the number of CAG repeats. The conversion criteria were met with the mean square error of 76.598. The value of parameters are as follows: $A = 1171.583$, $a = 0.091$.

20

EXAMPLE 1

Physical Map of the SCA2 region

BAC library construction of total human genomic DNA was performed as described in Shizuya et al., *Proc. Natl. Acad. Sci. USA* 89:8794-8797 (1992). BAC clones were screened by PCR using STSs (D12S1228, S29, S32, S33). Insert size of clones was measured by running pulsed-field gel electrophoresis after digesting DNA with NotI.

30

The marker AFMa128yf1 (D12S1332) which was non-recombinant in several SCA2 pedigrees served as the starting point to assemble a PAC contig. This was done by screening PCR pools of a 3x human PAC library (Ioannou et al., 1994). Two clones were positive for this STS (Fig. 1). Single copy sequences from PAC ends were obtained from P168L1 and used to extend this contig.

35

Subsequent 'walking steps, however, were undertaken by hybridizing PCR-generated STS fragments to gridded membranes of the 3x PAC library and the 1x total human genome BAC library (Research Genetics).

5

In a similar fashion, a second contig was established starting with the telomeric flanking marker AFM154tc5 (D12S1333). A total of two clones were identified by screening of PCR pools. After several walking steps, overlap of the two contigs was established by shared STSs (Fig. 1) and by shared restriction fragments (data not shown). All STSs shown in Fig. 1 were mapped back to human chromosome 12 by PCR analysis of a human/Chinese hamster somatic hybrid cell line, HHW582, which contains CHR 12 as the only human chromosome, and by analysis of a chromosome 12 specific lambda library, LL12NS01 (both from Coriell Cell Repositories). Map position in 21q24.1 for clones B295C05, P191C5 and P65I22 was confirmed using FISH (Fig. 1b).

At the same time contigs were constructed for the other flanking markers AFM240wel (D12S1328), AFM291xe9 (D12S1329), and markers WI-4176 and WI-6850 (data not shown). These contigs did not overlap with one another, nor with the AFMa128yf1/AFM154tc5 contig.

All PAC and BAC clones were sized by pulsed-field electrophoresis after digestion with NotI. Overlap of clones was initially determined by shared STS content, and subsequently confirmed by hybridization of selected clones to Southern blots of NotI/XbaI digests of clones.

The dense localization of STSs allowed the precise positioning of YACs that had been identified by screening of PCR pools of the CEPH mega-YAC library with either AFMa128yf1 or AFM154tc5. The only YAC that was

positive for both AFMa128yf1 (D12S1332) and AFM154tc5, Y884_h_11, contained an approximately 200 kb interstitial deletion. A small portion of this deletion was not covered by any of the other YAC clones.

5

EXAMPLE 2

Identification of SCA2-related trinucleotide repeats

Since we had observed marked anticipation in one pedigree with SCA2, we identified clones containing trinucleotide repeats. EcoRI digests of a minimal tiling path of PAC clones were hybridized with a (CAG)₁₀ nucleotide, as well as other trinucleotide permutations. Three CAG positive bands of distinct sizes were identified in the contig.

PAC clone P65I22 was digested with Sau3A and subcloned into the pBluescript SK (+) phagemid (Stratagene). After transfection into DH5 α , bacterial colonies were screened for poly-CAG containing inserts using the methods described above. Positive clones were sequenced using the Circum Vent cycle sequencing kit (New England Biolabs) with end-labeled T3 and T7 primers. However, no reliable sequence could be obtained from the initial plasmid PL65I22. Therefore, this plasmid was digested with BssHII, recloned into the pBluescript plasmid, and CAG-positive clones sequenced with primers corresponding to the following nucleotides of the vector sequence (primer A: 828-848, primer B: 547-565). The sequence of this plasmid, designated PL65I22B, allowed the generation of primers SCA2-A and SCA2-B, which were used to confirm the sequence flanking the CAG repeat.

Plasmid PL65I22B containing an extended CAG repeat that appeared to be embedded into a long open reading frame (ORF) (Figure 2; SEQ ID NO:1). Sequence analysis of this plasmid appeared to be extremely

difficult due to the abundant presence of premature terminations (see below). The CAG repeat in PL65I22B was twice interrupted and had the following structure (CAG)₈CAA(CAG)₄CAA(CAG)₈. Four additional PAC clones and one BAC clone contained the SCA2 repeat, and all clones had 22 repeats with two CAA interruptions. Analysis of the genomic DNA sequence flanking the CAG repeat suggested the presence of an open reading frame (see also Figure 6) and a potential splice site 3' of the CAG repeat (vertical arrow in Figure 2).

The difficulties encountered in sequencing this region suggested that stable secondary structures might be formed in this GC-rich region. Previous analysis of trinucleotide repeats predisposed to expansion had suggested that these regions are predicted to form hairpin structures. We used an up-dated version of the DNA-FOLD Program (SantaLucia et al., 1996, Biochemistry, 35:3555-3562) for secondary structure predictions.

Subsequent analysis of the sequence flanking the CAG repeat using the OLIGO Program indicated that it contained several palindromic sequences predicted to form hairpin loops. Despite the predicted hairpin structures sufficient sequence information was generated to design primers flanking the CAG repeat for the PCR analysis of patient samples.

Example 3

Genomic analysis of an extended CAG SCA2 repeat

Using primer pairs SCA2-A and B, genomic DNAs from normal controls and SCA2 patients were amplified and separated by agarose gel electrophoresis. The best results were obtained at an annealing temperature of 63°C with denaturation times of 90 sec.

Eighty ng each of primers SCA2-A (5'-GGG CCC CTC ACC ATG TCG-3') and SCA2-B (5'-CGG GCT TGC GGA CAT TGG-3') were added to 20 ng of human DNA with standard PCR buffer and nucleotide concentrations. After an
5 initial denaturation at 95°C for 5 minutes, 35 cycles were repeated with denaturation at 96°C for 1.5 minutes, an annealing temperature of 63°C for 30 seconds, extension at 72°C for 1.5 minutes, and a final extension of 5 minutes at 72°C.

10

PCR products obtained by PCR amplification of genomic DNAs were separated by electrophoresis through 2% agarose gels in 1x TBE buffer at 10 V/cm. Gels were transferred to nylon membranes (MSI, Westborough, MA)
15 using standard procedures for Southern blotting. Membranes were hybridized with a (CAG)₁₀ oligonucleotide and processed as described above.

On agarose electrophoresis, a single band of
20 approximately 130 bp was detected in 20 normal individuals, although occasionally two closely spaced bands could be observed. In contrast, all 15 patients with SCA2 from 3 independent families showed one allele in the normal size range and a larger allele ranging from
25 approximately 190 to 250 bp. Southern blot analysis confirmed that both alleles contained CAG repeats.

To determine the exact sizes of amplified fragments, DNAs from SCA2 patients and 50 normal
30 individuals were amplified and PCR products separated by polyacrylamide gel electrophoresis. A common allele of 22 repeats and a less frequent allele of 23 repeats were observed on normal chromosomes (Figure 3). The allele frequencies were 0.92 for the smaller and 0.08 for the
35 larger allele. In patients from three independent SCA2 pedigrees, however, extended alleles ranging from 36 to 52 repeats were observed (Figure 3). Once expanded to

the pathologic range, the SCA2 repeat was moderately unstable and further expansion by 2 to 9 repeat units was observed during meiosis (Figure 3). There was great variability of the age of onset for a given repeat length, especially for disease alleles with 36-40 repeats (Figure 4). Due to the heterogeneous variance of age of onset we used non-linear regression, and an exponential function was successfully fitted (see methods and Figure 4). The smallest expansion of 36 repeats was seen in two men with disease onset at ages 37 and 44. The longest expansion of 52 repeats was seen in a boy with disease onset at 9 years of age.

Sequence analysis of ten normal alleles revealed that the common normal allele with 22 repeats contained the two CAA interruptions that were also detected in plasmid PL65I22B. The less frequent normal allele with 23 repeats had lost the 5' CAA interruption, and contained an additional CAG repeat at the 5'-end of the repeat. In three expanded alleles that were isolated from SCA2 patients the CAG repeat lacked any interruptions.

To determine the frequency of mutation in the SCA2 gene in non-Portuguese patients we screened DNAs from 45 independent families with autosomal dominant SCAs. Expansion of the SCA2 repeat was detected in six families. In this set of families, SCA2 expansion was twice as common as expansion in the SCA1 gene. In addition to individuals with a 'typical' SCA phenotype, expansion of the SCA2 repeat was detected in a pedigree with a MJD phenotype and one family with SCA and marked dementia.

EXAMPLE 4

Isolation of human SCA2 cDNA

cDNA library screen: 32 P-labeled probes were generated by
5 PCR amplification of plasmid P65I22B using the following
primer pair: 65A3: 5'CCGCGGCTGCCAATGTCC, 65B5:
5'GTAACCGTTTCGGCGCCCG. A second probe was generated using
primers 65A6: 5'GGCTCCCGGCGGCTCCTT; 65B6:
5'TGCTGCTGCTGCTGGGGCTTCAG. Screening of the trisomy 21
10 fetal brain cDNA library and the Stratagene adult human
frontal cortex cDNA Lambda Zap II library was performed
using the amplification products generated from plasmid
P65I22B. Phages were plated to an average density of 1×10^5
per 150 cm² plate. Plaque lifts of 20 plates (2×10^6
15 phages) were made using duplicated nylon membranes
(Duralose-UV, Stratagene). Hybridization and excision
were performed according to the manufacturer's protocol.
Hybridized membranes were washed to a final stringency of
0.2x SSC, 0.1x SDS at 65C. The filters were exposed
20 overnight onto X-ray film. Excised phagemids were grown
overnight in 5ml LB medium containing 50 ug/ml of
ampicillin.

Using PCR-generated fragments containing
25 nucleotides 39-237 and 262 to 397 (according to the
sequence shown in Figure 2) we initially screened a human
adult frontal cortex library (Stratagene). Through
screening of 0.8×10^6 clones, two positive clones, S1 and
S2, were identified. To obtain additional clones, 2×10^6
30 clones of a human fetal brain library generated from a
fetus with trisomy 21 (Yamakawa et al., 1995, Hum. Mol.
Genet., 4:709-716) were screened using the same PCR-
generated fragments. A total of 15 clones were obtained,
all of which were partially sequenced to determine
35 alignment of clones. These clones appeared to belong to
a total of two classes of clones (designated F1.1 through
F1.7 and F2.1 through F2.8) that contained long portions

of the 3' untranslated region and a poly-A tail (Figure 5). Both classes of clones extended 40 and 265 bp 5' of the CAG repeat in the coding region of the SCA2 gene.

5 To obtain cDNA sequence for the 5' end of the SCA2 coding region, placental poly-T selected placental mRNAs (Clontech) were transcribed with MMLV reverse transcriptase and amplified with the following primer pairs: SCA2-A30: 5'CCGCCCCGCTCCTCACGTGT, SCA2-A31:
10 5'ACCCCCGAGAAAGCAACC; SCA2-B30: 5'-CCGTTGCCGTTGCTACCA. The sequences for primers SCA2-A30 and A31 were obtained from genomic sequence, and are located 5' to the stop codon preceding the putative initiator methionine. The sequence for SCA2-B30 was obtained from the 5' end of
15 cDNA clones F1.1 and F1.2. The amplicons obtained by RT-PCR were directly sequenced.

 The composite of the human SCA2 cDNA sequence assembled from several overlapping cDNA clones is shown
20 in Figure 6 (SEQ ID NO:2). The longest open reading frame consists of 3936 bp and ends with a TAA termination codon. The stop codon is followed by 364 bp of 3' untranslated sequence. The CAG repeat is located in the 5'end of the coding region. The putative translation
25 start site follows an in frame stop codon located 78 bp upstream. The predicted molecular weight for the SCA2 translation product is 140.1 kDa with the CAG trinucleotide repeat predicted to code for glutamine. In analogy to the SCA1 gene product, we propose the name
30 ataxin-2 for the SCA2 gene product.

 The cDNA sequence was compared against the GenBank database using the FASTA sequence alignment algorithms and the TIGR database. The predicted protein
35 sequence was compared against the SwissProt database and the predicted translation products of the GenBank database. These searches revealed no significant

similarities to genes of known function except for limited homologies to the GLI-Krueppel related protein YY1 (nucleotides 45 to 586, odds against chance occurrence 6.6×10^{-7}).

5

However, significant similarities were detected with two partial cDNA transcripts in the TIGR database (THC148678, H03566, odds against chance similarity $<10^{-31}$). Complete sequence analysis of these cDNA clones
10 (purchased from ATCC) revealed significant homologies with ataxin-2. This protein was named ataxin-2 related protein (A2RP). The region showing the most significant homology including a domain of 42 amino acids with 86% identity (codons 243-284 of the consensus sequence) is
15 shown in Figure 7. This domain is also 100% conserved in mouse ataxin-2. Despite the significant homologies, the polyglutamine tract in ataxin-2 was replaced with an interrupted polyproline tract in the related A2RP human protein and was reduced to one glutamine in the mouse
20 SCA2 homologue (see Figure 7).

Example 6

RT-PCR and Northern blot analysis:

25 RNA isolation and reverse transcription was carried out using well-known methods (Huynh et al., 1994, Hum. Mol. Genet., 3:1075-1079). RNAs were isolated from lymphoblastoid cell lines established from patients and unrelated spouses in the FS pedigree with SCA2 (Pulst et al., 1993, Nat. Genet., 5:8-10). Multiple tissue
30 Northern blots were purchased from Clontech. For amplification, primers located in two exons (SCA-A and SCA-B14, see also Figure 6) were chosen so that genomic DNA was not amplified. The sequence for SCA-B14 was:
35 5'TTCTCATGTGCGGCATCAAG.

Using RT-PCR, it was determined that the SCA2 CAG repeat was transcribed in lymphoblastoid cell lines. In cDNAs from SCA2 patients, transcription from both the normal and the expanded allele was detected using
5 oligonucleotide primers that flank the repeat. By Northern blot analysis, the SCA2 gene was determined to be widely expressed. A strong signal corresponding to a 4.5 kb transcript was detected in all brain regions examined. This transcript was also detected in RNAs
10 isolated from heart, placenta, liver, skeletal muscle, and pancreas. Little transcript was detected in lung and no transcription was detectable in kidney. A much fainter transcript of 7.5 kb could be seen in RNAs isolated from some brain regions and in some peripheral
15 tissues.

EXAMPLE 7

Isolation of mouse SCA2 cDNA

20 To identify mouse SCA2 cDNA clones, the Stratagene Lambda ZAP newborn mouse brain cDNA library was screened with a human SCA2 cDNA clone. Six clones were identified and sequenced. A full-length mouse SCA2 cDNA is set forth in SEQ ID NO:4.

25

SUMMARY OF SEQUENCES

SEQ ID NO:1 is the genomic nucleic acid sequence set forth in Figure 2.

30

SEQ ID NO:2 is the nucleic acid sequence (and the deduced amino acid sequence) of a cDNA encoding a human-derived SCA2 protein of the present invention (also set forth in Figure 6).

35

SEQ ID NO:3 is the deduced amino acid sequence of the human-derived SCA2 protein set forth in SEQ ID NO:2.

5 SEQ ID NO:4 is the nucleic acid sequence (and the deduced amino acid sequence) of a cDNA encoding a mouse-derived SCA2 protein of the present invention.

10 SEQ ID NO:5 is the deduced amino acid sequence of the mouse-derived SCA2 protein set forth in SEQ ID NO:4.

SEQUENCE LISTING

(1) GENERAL INFORMATION:

- (i) APPLICANT: CEDARS-SINAI MEDICAL CENTER
- (ii) TITLE OF INVENTION: NUCLEIC ACID ENCODING SPINOCEREBELLAR ATAXIA-2 AND PRODUCTS RELATED THERETO
- (iii) NUMBER OF SEQUENCES: 5
- (iv) CORRESPONDENCE ADDRESS:
 - (A) ADDRESSEE: Campbell & Flores LLP
 - (B) STREET: 4370 La Jolla Village Drive, Suite 700
 - (C) CITY: San Diego
 - (D) STATE: California
 - (E) COUNTRY: USA
 - (F) ZIP: 92122
- (v) COMPUTER READABLE FORM:
 - (A) MEDIUM TYPE: Floppy disk
 - (B) COMPUTER: IBM PC compatible
 - (C) OPERATING SYSTEM: PC-DOS/MS-DOS
 - (D) SOFTWARE: PatentIn Release #1.0, Version #1.25
- (viii) ATTORNEY/AGENT INFORMATION:
 - (A) NAME: Ramos, Robert T.
 - (B) REGISTRATION NUMBER: 37,915
 - (C) REFERENCE/DOCKET NUMBER: FP CE 2563
- (ix) TELECOMMUNICATION INFORMATION:
 - (A) TELEPHONE: (619) 535-9001
 - (B) TELEFAX: (619) 535-8949

(2) INFORMATION FOR SEQ ID NO:1:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 516 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: both
 - (D) TOPOLOGY: both
- (ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:1:

TTGGTAGCAA CGGAAACGGC GCGGGCGCGT TTCGGCCCCG CTCCCGGCGG CTCCTTGGTC	60
TCGGCGGGCC TCCCCGCCCC TTCGTGTCG TCCTTCTCCC CCTCGCCAGC CCGGGCGCCC	120
CTCCGGCCGC GCCAACCCGC GCCTCCCCGC TCGGCGCCCC TCGGTCCCCG CCGCGTTCCG	180

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GCGTCTCCTT GCGCGCCCCG GCTCCCGGCT GTCCCCGCCC GCGGTGCGAG CCGGTGTATG      240
GGCCCCTCAC CATGTCGCTG AAGCCCCAGC AGCAGCAGCA GCAGCAGCAG CAACAGCAGC      300
AGCAGCAACA GCAGCAGCAG CAGCAGCAGC AGCCGCCGCC CGCGGCTGCC AATGTCCGCA      360
AGCCCGGCGG CAGCGGCCTT CTAGCGTCGC CCGCCGCCGC GCCTTCGCCG TCCTCGTCCT      420
CGGTCTCCTC GTCCTCGGCC ACGGCTCCCT CCTCGGTGGT CGCGGCGACC TCCGGCGGCG      480
GGAGGCCCGG CCTGGGCAGG TGGGTGTCGG CACCCC                                516

```

(2) INFORMATION FOR SEQ ID NO:2:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 4481 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: both
- (D) TOPOLOGY: both

(ii) MOLECULE TYPE: cDNA

(ix) FEATURE:

- (A) NAME/KEY: CDS
- (B) LOCATION: 163..4101

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:2:

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ACCCCCGAGA AAGCAACCCA GCGCGCCGCC CGCTCCTCAC GTGTCCCTCC CGGCCCCGGG      60
GCCACCTCAC GTTCTGCTTC CGTCTGACCC CTCCGACTTC CGGTAAAGAG TCCCTATCCG      120
CACCTCCGCT CCCACCCGGC GCCTCGGCGC GCCCGCCCTC CG ATG CGC TCA GCG      174
                                     Met Arg Ser Ala
                                     1
GCC GCA GCT CCT CGG AGT CCC GCG GTG GCC ACC GAG TCT CGC CGC TTC      222
Ala Ala Ala Pro Arg Ser Pro Ala Val Ala Thr Glu Ser Arg Arg Phe
  5                      10                      15                      20
GCC GCA GCC AGG TGG CCC GGG TGG CGC TCG CTC CAG CGG CCG GCG CGG      270
Ala Ala Ala Arg Trp Pro Gly Trp Arg Ser Leu Gln Arg Pro Ala Arg
                25                      30                      35
CGG AGC GGG CGG GGC GGC GGT GGC GCG GCC CCG GGA CCG TAT CCC TCC      318
Arg Ser Gly Arg Gly Gly Gly Gly Ala Ala Pro Gly Pro Tyr Pro Ser
                40                      45                      50
GCC GCC CCT CCC CCG CCC GGC CCC GGC CCC CCT CCC TCC CGG CAG AGC      366
Ala Ala Pro Pro Pro Pro Gly Pro Gly Pro Pro Pro Ser Arg Gln Ser
                55                      60                      65

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TCG CCT CCC TCC GCC TCA GAC TGT TTT GGT AGC AAC GGC AAC GGC GGC	414
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70 75 80	
GGC GCG TTT CGG CCC GGC TCC CGG CGG CTC CTT GGT CTC GGC GGG CCT	462
Gly Ala Phe Arg Pro Gly Ser Arg Arg Leu Leu Gly Leu Gly Gly Pro	
85 90 95 100	
CCC CGC CCC TTC GTC GTC GTC CTT CTC CCC CTC GCC AGC CCG GGC GCC	510
Pro Arg Pro Phe Val Val Val Leu Leu Pro Leu Ala Ser Pro Gly Ala	
105 110 115	
CCT CCG GCC GCG CCA ACC CGC GCC TCC CCG CTC GGC GCC CGT GCG TCC	558
Pro Pro Ala Ala Pro Thr Arg Ala Ser Pro Leu Gly Ala Arg Ala Ser	
120 125 130	
CCG CCG CGT TCC GGC GTC TCC TTG GCG CGC CCG GCT CCC GGC TGT CCC	606
Pro Pro Arg Ser Gly Val Ser Leu Ala Arg Pro Ala Pro Gly Cys Pro	
135 140 145	
CGC CCG GCG TGC GAG CCG GTG TAT GGG CCC CTC ACC ATG TCG CTG AAG	654
Arg Pro Ala Cys Glu Pro Val Tyr Gly Pro Leu Thr Met Ser Leu Lys	
150 155 160	
CCC CAG CAG CAG CAG CAG CAG CAG CAG CAA CAG CAG CAG CAG CAA CAG	702
Pro Gln Gln Gln Gln Gln Gln Gln Gln Gln Gln Gln Gln Gln Gln	
165 170 175 180	
CAG CAG CAG CAG CAG CAG CAG CCG CCG CCC GCG GCT GCC AAT GTC CGC	750
Gln Gln Gln Gln Gln Gln Gln Pro Pro Pro Ala Ala Ala Asn Val Arg	
185 190 195	
AAG CCC GGC GGC AGC GGC CTT CTA GCG TCG CCC GCC GCC GCG CCT TCG	798
Lys Pro Gly Gly Ser Gly Leu Leu Ala Ser Pro Ala Ala Ala Pro Ser	
200 205 210	
CCG TCC TCG TCC TCG GTC TCC TCG TCC TCG GCC ACG GCT CCC TCC TCG	846
Pro Ser Ser Ser Ser Val Ser Ser Ser Ser Ala Thr Ala Pro Ser Ser	
215 220 225	
GTG GTC GCG GCG ACC TCC GGC GGC GGG AGG CCC GGC CTG GGC AGA GGT	894
Val Val Ala Ala Thr Ser Gly Gly Gly Arg Pro Gly Leu Gly Arg Gly	
230 235 240	
CGA AAC AGT AAC AAA GGA CTG CCT CAG TCT ACG ATT TCT TTT GAT GGA	942
Arg Asn Ser Asn Lys Gly Leu Pro Gln Ser Thr Ile Ser Phe Asp Gly	
245 250 255 260	
ATC TAT GCA AAT ATG AGG ATG GTT CAT ATA CTT ACA TCA GTT GTT GGC	990
Ile Tyr Ala Asn Met Arg Met Val His Ile Leu Thr Ser Val Val Gly	
265 270 275	
TCC AAA TGT GAA GTA CAA GTG AAA AAT GGA GGT ATA TAT GAA GGA GTT	1038
Ser Lys Cys Glu Val Gln Val Lys Asn Gly Gly Ile Tyr Glu Gly Val	
280 285 290	

TTT AAA ACT TAC AGT CCG AAG TGT GAT TTG GTA CTT GAT GCC GCA CAT	1086
Phe Lys Thr Tyr Ser Pro Lys Cys Asp Leu Val Leu Asp Ala Ala His	
295 300 305	
GAG AAA AGT ACA GAA TCC AGT TCG GGG CCG AAA CGT GAA GAA ATA ATG	1134
Glu Lys Ser Thr Glu Ser Ser Ser Gly Pro Lys Arg Glu Glu Ile Met	
310 315 320	
GAG AGT ATT TTG TTC AAA TGT TCA GAC TTT GTT GTG GTA CAG TTT AAA	1182
Glu Ser Ile Leu Phe Lys Cys Ser Asp Phe Val Val Val Gln Phe Lys	
325 330 335 340	
GAT ATG GAC TCC AGT TAT GCA AAA AGA GAT GCT TTT ACT GAC TCT GCT	1230
Asp Met Asp Ser Ser Tyr Ala Lys Arg Asp Ala Phe Thr Asp Ser Ala	
345 350 355	
ATC AGT GCT AAA GTG AAT GGC GAA CAC AAA GAG AAG GAC CTG GAG CCC	1278
Ile Ser Ala Lys Val Asn Gly Glu His Lys Glu Lys Asp Leu Glu Pro	
360 365 370	
TGG GAT GCA GGT GAA CTC ACA GCC AAT GAG GAA CTT GAG GCT TTG GAA	1326
Trp Asp Ala Gly Glu Leu Thr Ala Asn Glu Glu Leu Glu Ala Leu Glu	
375 380 385	
AAT GAC GTA TCT AAT GGA TGG GAT CCC AAT GAT ATG TTT CGA TAT AAT	1374
Asn Asp Val Ser Asn Gly Trp Asp Pro Asn Asp Met Phe Arg Tyr Asn	
390 395 400	
GAA GAA AAT TAT GGT GTA GTG TCT ACG TAT GAT AGC AGT TTA TCT TCG	1422
Glu Glu Asn Tyr Gly Val Val Ser Thr Tyr Asp Ser Ser Leu Ser Ser	
405 410 415 420	
TAT ACA GTG CCC TTA GAA AGA GAT AAC TCA GAA GAA TTT TTA AAA CGG	1470
Tyr Thr Val Pro Leu Glu Arg Asp Asn Ser Glu Glu Phe Leu Lys Arg	
425 430 435	
GAA GCA AGG GCA AAC CAG TTA GCA GAA GAA ATT GAG TCA AGT GCC CAG	1518
Glu Ala Arg Ala Asn Gln Leu Ala Glu Glu Ile Glu Ser Ser Ala Gln	
440 445 450	
TAC AAA GCT CGA GTG GCC CTG GAA AAT GAT GAT AGG AGT GAG GAA GAA	1566
Tyr Lys Ala Arg Val Ala Leu Glu Asn Asp Asp Arg Ser Glu Glu Glu	
455 460 465	
AAA TAC ACA GCA GTT CAG AGA AAT TCC AGT GAA CGT GAG GGG CAC AGC	1614
Lys Tyr Thr Ala Val Gln Arg Asn Ser Ser Glu Arg Glu Gly His Ser	
470 475 480	
ATA AAC ACT AGG GAA AAT AAA TAT ATT CCT CCT GGA CAA AGA AAT AGA	1662
Ile Asn Thr Arg Glu Asn Lys Tyr Ile Pro Pro Gly Gln Arg Asn Arg	
485 490 495 500	
GAA GTC ATA TCC TGG GGA AGT GGG AGA CAG AAT TCA CCG CGT ATG GGC	1710
Glu Val Ile Ser Trp Gly Ser Gly Arg Gln Asn Ser Pro Arg Met Gly	
505 510 515	

CAG CCT GGA TCG GGC TCC ATG CCA TCA AGA TCC ACT TCT CAC ACT TCA	1758
Gln Pro Gly Ser Gly Ser Met Pro Ser Arg Ser Thr Ser His Thr Ser	
520 525 530	
GAT TTC AAC CCG AAT TCT GGT TCA GAC CAA AGA GTA GTT AAT GGA GGT	1806
Asp Phe Asn Pro Asn Ser Gly Ser Asp Gln Arg Val Val Asn Gly Gly	
535 540 545	
GTT CCC TGG CCA TCG CCT TGC CCA TCT CCT TCC TCT CGC CCA CCT TCT	1854
Val Pro Trp Pro Ser Pro Cys Pro Ser Pro Ser Ser Arg Pro Pro Ser	
550 555 560	
CGC TAC CAG TCA GGT CCC AAC TCT CTT CCA CCT CGG GCA GCC ACC CCT	1902
Arg Tyr Gln Ser Gly Pro Asn Ser Leu Pro Pro Arg Ala Ala Thr Pro	
565 570 575 580	
ACA CGG CCG CCC TCC AGG CCC CCC TCG CGG CCA TCC AGA CCC CCG TCT	1950
Thr Arg Pro Pro Ser Arg Pro Pro Ser Arg Pro Ser Arg Pro Ser	
585 590 595	
CAC CCC TCT GCT CAT GGT TCT CCA GCT CCT GTC TCT ACT ATG CCT AAA	1998
His Pro Ser Ala His Gly Ser Pro Ala Pro Val Ser Thr Met Pro Lys	
600 605 610	
CGC ATG TCT TCA GAA GGG CCT CCA AGG ATG TCC CCA AAG GCC CAG CGA	2046
Arg Met Ser Ser Glu Gly Pro Pro Arg Met Ser Pro Lys Ala Gln Arg	
615 620 625	
CAT CCT CGA AAT CAC AGA GTT TCT GCT GGG AGG GGT TCC ATA TCC AGT	2094
His Pro Arg Asn His Arg Val Ser Ala Gly Arg Gly Ser Ile Ser Ser	
630 635 640	
GGC CTA GAA TTT GTA TCC CAC AAC CCA CCC AGT GAA GCA GCT ACT CCT	2142
Gly Leu Glu Phe Val Ser His Asn Pro Pro Ser Glu Ala Ala Thr Pro	
645 650 655 660	
CCA GTA GCA AGG ACC AGT CCC TCG GGG GGA ACG TGG TCA TCA GTG GTC	2190
Pro Val Ala Arg Thr Ser Pro Ser Gly Gly Thr Trp Ser Ser Val Val	
665 670 675	
AGT GGG GTT CCA AGA TTA TCC CCT AAA ACT CAT AGA CCC AGG TCT CCC	2238
Ser Gly Val Pro Arg Leu Ser Pro Lys Thr His Arg Pro Arg Ser Pro	
680 685 690	
AGA CAG AAC AGT ATT GGA AAT ACC CCC AGT GGG CCA GTT CTT GCT TCT	2286
Arg Gln Asn Ser Ile Gly Asn Thr Pro Ser Gly Pro Val Leu Ala Ser	
695 700 705	
CCC CAA GCT GGT ATT ATT CCA ACT GAA GCT GTT GCC ATG CCT ATT CCA	2334
Pro Gln Ala Gly Ile Ile Pro Thr Glu Ala Val Ala Met Pro Ile Pro	
710 715 720	
GCT GCA TCT CCT ACG CCT GCT AGT CCT GCA TCG AAC AGA GCT GTT ACC	2382
Ala Ala Ser Pro Thr Pro Ala Ser Pro Ala Ser Asn Arg Ala Val Thr	
725 730 735 740	

CCT TCT AGT GAG GCT AAA GAT TCC AGG CTT CAA GAT CAG AGG CAG AAC	2430
Pro Ser Ser Glu Ala Lys Asp Ser Arg Leu Gln Asp Gln Arg Gln Asn	
745 750 755	
TCT CCT GCA GGG AAT AAA GAA AAT ATT AAA CCC AAT GAA ACA TCA CCT	2478
Ser Pro Ala Gly Asn Lys Glu Asn Ile Lys Pro Asn Glu Thr Ser Pro	
760 765 770	
AGC TTC TCA AAA GCT GAA AAC AAA GGT ATA TCA CCA GTT GTT TCT GAA	2526
Ser Phe Ser Lys Ala Glu Asn Lys Gly Ile Ser Pro Val Val Ser Glu	
775 780 785	
CAT AGA AAA CAG ATT GAT GAT TTA AAG AAA TTT AAG AAT GAT TTT AGG	2574
His Arg Lys Gln Ile Asp Asp Leu Lys Lys Phe Lys Asn Asp Phe Arg	
790 795 800	
TTA CAG CCA AGT TCT ACT TCT GAA TCT ATG GAT CAA CTA CTA AAC AAA	2622
Leu Gln Pro Ser Ser Thr Ser Glu Ser Met Asp Gln Leu Leu Asn Lys	
805 810 815 820	
AAT AGA GAG GGA GAA AAA TCA AGA GAT TTG ATC AAA GAC AAA ATT GAA	2670
Asn Arg Glu Gly Glu Lys Ser Arg Asp Leu Ile Lys Asp Lys Ile Glu	
825 830 835	
CCA AGT GCT AAG GAT TCT TTC ATT GAA AAT AGC AGC AGC AAC TGT ACC	2718
Pro Ser Ala Lys Asp Ser Phe Ile Glu Asn Ser Ser Ser Asn Cys Thr	
840 845 850	
AGT GGC AGC AGC AAG CCG AAT AGC CCC AGC ATT TCC CCT TCA ATA CTT	2766
Ser Gly Ser Ser Lys Pro Asn Ser Pro Ser Ile Ser Pro Ser Ile Leu	
855 860 865	
AGT AAC ACG GAG CAC AAG AGG GGA CCT GAG GTC ACT TCC CAA GGG GTT	2814
Ser Asn Thr Glu His Lys Arg Gly Pro Glu Val Thr Ser Gln Gly Val	
870 875 880	
CAG ACT TCC AGC CCA GCA TGT AAA CAA GAG AAA GAC GAT AAG GAA GAG	2862
Gln Thr Ser Ser Pro Ala Cys Lys Gln Glu Lys Asp Asp Lys Glu Glu	
885 890 895 900	
AAG AAA GAC GCA GCT GAG CAA GTT AGG AAA TCA ACA TTG AAT CCC AAT	2910
Lys Lys Asp Ala Ala Glu Gln Val Arg Lys Ser Thr Leu Asn Pro Asn	
905 910 915	
GCA AAG GAG TTC AAC CCA CGT TCC TTC TCT CAG CCA AAG CCT TCT ACT	2958
Ala Lys Glu Phe Asn Pro Arg Ser Phe Ser Gln Pro Lys Pro Ser Thr	
920 925 930	
ACC CCA ACT TCA CCT CGG CCT CAA GCA CAA CCT AGC CCA TCT ATG GTG	3006
Thr Pro Thr Ser Pro Arg Pro Gln Ala Gln Pro Ser Pro Ser Met Val	
935 940 945	
GGT CAT CAA CAG CCA ACT CCA GTT TAT ACT CAG CCT GTT TGT TTT GCA	3054
Gly His Gln Gln Pro Thr Pro Val Tyr Thr Gln Pro Val Cys Phe Ala	
950 955 960	

CCA AAT ATG ATG TAT CCA GTC CCA GTG AGC CCA GGC GTG CAA CCT TTA	3102
Pro Asn Met Met Tyr Pro Val Pro Val Ser Pro Gly Val Gln Pro Leu	
965 970 975 980	
TAC CCA ATA CCT ATG ACG CCC ATG CCA GTG AAT CAA GCC AAG ACA TAT	3150
Tyr Pro Ile Pro Met Thr Pro Met Pro Val Asn Gln Ala Lys Thr Tyr	
985 990 995	
AGA GCA GTA CCA AAT ATG CCC CAA CAG CGG CAA GAC CAG CAT CAT CAG	3198
Arg Ala Val Pro Asn Met Pro Gln Gln Arg Gln Asp Gln His His Gln	
1000 1005 1010	
AGT GCC ATG ATG CAC CCA GCG TCA GCA GCG GGC CCA CCG ATT GCA GCC	3246
Ser Ala Met Met His Pro Ala Ser Ala Ala Gly Pro Pro Ile Ala Ala	
1015 1020 1025	
ACC CCA CCA GCT TAC TCC ACG CAA TAT GTT GCC TAC AGT CCT CAG CAG	3294
Thr Pro Pro Ala Tyr Ser Thr Gln Tyr Val Ala Tyr Ser Pro Gln Gln	
1030 1035 1040	
TTC CCA AAT CAG CCC CTT GTT CAG CAT GTG CCA CAT TAT CAG TCT CAG	3342
Phe Pro Asn Gln Pro Leu Val Gln His Val Pro His Tyr Gln Ser Gln	
1045 1050 1055 1060	
CAT CCT CAT GTC TAT AGT CCT GTA ATA CAG GGT AAT GCT AGA ATG ATG	3390
His Pro His Val Tyr Ser Pro Val Ile Gln Gly Asn Ala Arg Met Met	
1065 1070 1075	
GCA CCA CCA ACA CAC GCC CAG CCT GGT TTA GTA TCT TCT TCA GCA ACT	3438
Ala Pro Pro Thr His Ala Gln Pro Gly Leu Val Ser Ser Ser Ala Thr	
1080 1085 1090	
CAG TAC GGG GCT CAT GAG CAG ACG CAT GCG ATG TAT GCA TGT CCC AAA	3486
Gln Tyr Gly Ala His Glu Gln Thr His Ala Met Tyr Ala Cys Pro Lys	
1095 1100 1105	
TTA CCA TAC AAC AAG GAG ACA AGC CCT TCT TTC TAC TTT GCC ATT TCC	3534
Leu Pro Tyr Asn Lys Glu Thr Ser Pro Ser Phe Tyr Phe Ala Ile Ser	
1110 1115 1120	
ACG GGC TCC CTT GCT CAG CAG TAT GCG CAC CCT AAC GCT ACC CTG CAC	3582
Thr Gly Ser Leu Ala Gln Gln Tyr Ala His Pro Asn Ala Thr Leu His	
1125 1130 1135 1140	
CCA CAT ACT CCA CAC CCT CAG CCT TCA GCT ACC CCC ACT GGA CAG CAG	3630
Pro His Thr Pro His Pro Gln Pro Ser Ala Thr Pro Thr Gly Gln Gln	
1145 1150 1155	
CAA AGC CAA CAT GGT GGA AGT CAT CCT GCA CCC AGT CCT GTT CAG CAC	3678
Gln Ser Gln His Gly Gly Ser His Pro Ala Pro Ser Pro Val Gln His	
1160 1165 1170	
CAT CAG CAC CAG GCC GCC CAG GCT CTC CAT CTG GCC AGT CCA CAG CAG	3726
His Gln His Gln Ala Ala Gln Ala Leu His Leu Ala Ser Pro Gln Gln	
1175 1180 1185	

CAG TCA GCC ATT TAC CAC GCG GGG CTT GCG CCA ACT CCA CCC TCC ATG Gln Ser Ala Ile Tyr His Ala Gly Leu Ala Pro Thr Pro Pro Ser Met 1190 1195 1200	3774
ACA CCT GCC TCC AAC ACG CAG TCG CCA CAG AAT AGT TTC CCA GCA GCA Thr Pro Ala Ser Asn Thr Gln Ser Pro Gln Asn Ser Phe Pro Ala Ala 1205 1210 1215 1220	3822
CAA CAG ACT GTC TTT ACG ATC CAT CCT TCT CAC GTT CAG CCG GCG TAT Gln Gln Thr Val Phe Thr Ile His Pro Ser His Val Gln Pro Ala Tyr 1225 1230 1235	3870
ACC AAC CCA CCC CAC ATG GCC CAC GTA CCT CAG GCT CAT GTA CAG TCA Thr Asn Pro Pro His Met Ala His Val Pro Gln Ala His Val Gln Ser 1240 1245 1250	3918
GGA ATG GTT CCT TCT CAT CCA ACT GCC CAT GCG CCA ATG ATG CTA ATG Gly Met Val Pro Ser His Pro Thr Ala His Ala Pro Met Met Leu Met 1255 1260 1265	3966
ACG ACA CAG CCA CCC GGC GGT CCC CAG GCC GCC CTC GCT CAA AGT GCA Thr Thr Gln Pro Pro Gly Gly Pro Gln Ala Ala Leu Ala Gln Ser Ala 1270 1275 1280	4014
CTA CAG CCC ATT CCA GTC TCG ACA ACA GCG CAT TTC CCC TAT ATG ACG Leu Gln Pro Ile Pro Val Ser Thr Thr Ala His Phe Pro Tyr Met Thr 1285 1290 1295 1300	4062
CAC CCT TCA GTA CAA GCC CAC CAC CAA CAG CAG TTG TAAGGCTGCC His Pro Ser Val Gln Ala His His Gln Gln Gln Leu 1305 1310	4108
CTGGAGGAAC CGAAAGGCCA AATTCCCTCC TCCCTTCTAC TGCTTCTACC AACTGGAAGC	4168
ACAGAAACT AGAATTTTCAT TTATTTTGT TTTAAATAT ATATGTTGAT TTCTTGTAAC	4228
ATCCAATAGG AATGCTAACA GTTCACTTGC AGTGGAAGAT ACTTGGACCG AGTAGAGGCA	4288
TTTAGGAACT TGGGGGCTAT TCCATAATTC CATATGCTGT TTCAGAGTCC CGCAGGTACC	4348
CCAGCTCTGC TTGCCGAAAC TGGAAGTTAT TTATTTTTTA ATAACCCTTG AAAGTCATGA	4408
ACACATCAGC TAGCAAAGA AGTAACAAGA GTGATTCTTG CTGCTATTAC TGCTAAAAAA	4468
AAAAAAAAAA AAA	4481

(2) INFORMATION FOR SEQ ID NO:3:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 1312 amino acids
- (B) TYPE: amino acid
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:3:

Met	Arg	Ser	Ala	Ala	Ala	Ala	Pro	Arg	Ser	Pro	Ala	Val	Ala	Thr	Glu	1	5	10	15
Ser	Arg	Arg	Phe	Ala	Ala	Ala	Arg	Trp	Pro	Gly	Trp	Arg	Ser	Leu	Gln	20	25	30	
Arg	Pro	Ala	Arg	Arg	Ser	Gly	Arg	Gly	Gly	Gly	Gly	Ala	Ala	Pro	Gly	35	40	45	
Pro	Tyr	Pro	Ser	Ala	Ala	Pro	Pro	Pro	Gly	Pro	Gly	Pro	Pro	Pro	50	55	60		
Ser	Arg	Gln	Ser	Ser	Pro	Pro	Ser	Ala	Ser	Asp	Cys	Phe	Gly	Ser	Asn	65	70	75	80
Gly	Asn	Gly	Gly	Gly	Ala	Phe	Arg	Pro	Gly	Ser	Arg	Arg	Leu	Leu	Gly	85	90	95	
Leu	Gly	Gly	Pro	Pro	Arg	Pro	Phe	Val	Val	Val	Leu	Leu	Pro	Leu	Ala	100	105	110	
Ser	Pro	Gly	Ala	Pro	Pro	Ala	Ala	Pro	Thr	Arg	Ala	Ser	Pro	Leu	Gly	115	120	125	
Ala	Arg	Ala	Ser	Pro	Pro	Arg	Ser	Gly	Val	Ser	Leu	Ala	Arg	Pro	Ala	130	135	140	
Pro	Gly	Cys	Pro	Arg	Pro	Ala	Cys	Glu	Pro	Val	Tyr	Gly	Pro	Leu	Thr	145	150	155	160
Met	Ser	Leu	Lys	Pro	Gln	Gln	Gln	Gln	Gln	Gln	Gln	Gln	Gln	Gln	Gln	165	170	175	
Gln	Gln	Gln	Gln	Gln	Gln	Gln	Gln	Gln	Gln	Gln	Pro	Pro	Pro	Ala	Ala	180	185	190	
Ala	Asn	Val	Arg	Lys	Pro	Gly	Gly	Ser	Gly	Leu	Leu	Ala	Ser	Pro	Ala	195	200	205	
Ala	Ala	Pro	Ser	Pro	Ser	Ser	Ser	Ser	Val	Ser	Ser	Ser	Ser	Ala	Thr	210	215	220	
Ala	Pro	Ser	Ser	Val	Val	Ala	Ala	Thr	Ser	Gly	Gly	Gly	Arg	Pro	Gly	225	230	235	240
Leu	Gly	Arg	Gly	Arg	Asn	Ser	Asn	Lys	Gly	Leu	Pro	Gln	Ser	Thr	Ile	245	250	255	
Ser	Phe	Asp	Gly	Ile	Tyr	Ala	Asn	Met	Arg	Met	Val	His	Ile	Leu	Thr	260	265	270	
Ser	Val	Val	Gly	Ser	Lys	Cys	Glu	Val	Gln	Val	Lys	Asn	Gly	Gly	Ile	275	280	285	

Tyr Glu Gly Val Phe Lys Thr Tyr Ser Pro Lys Cys Asp Leu Val Leu
290 295 300

Asp Ala Ala His Glu Lys Ser Thr Glu Ser Ser Ser Gly Pro Lys Arg
305 310 315 320

Glu Glu Ile Met Glu Ser Ile Leu Phe Lys Cys Ser Asp Phe Val Val
325 330 335

Val Gln Phe Lys Asp Met Asp Ser Ser Tyr Ala Lys Arg Asp Ala Phe
340 345 350

Thr Asp Ser Ala Ile Ser Ala Lys Val Asn Gly Glu His Lys Glu Lys
355 360 365

Asp Leu Glu Pro Trp Asp Ala Gly Glu Leu Thr Ala Asn Glu Glu Leu
370 375 380

Glu Ala Leu Glu Asn Asp Val Ser Asn Gly Trp Asp Pro Asn Asp Met
385 390 395 400

Phe Arg Tyr Asn Glu Glu Asn Tyr Gly Val Val Ser Thr Tyr Asp Ser
405 410 415

Ser Leu Ser Ser Tyr Thr Val Pro Leu Glu Arg Asp Asn Ser Glu Glu
420 425 430

Phe Leu Lys Arg Glu Ala Arg Ala Asn Gln Leu Ala Glu Glu Ile Glu
435 440 445

Ser Ser Ala Gln Tyr Lys Ala Arg Val Ala Leu Glu Asn Asp Asp Arg
450 455 460

Ser Glu Glu Glu Lys Tyr Thr Ala Val Gln Arg Asn Ser Ser Glu Arg
465 470 475 480

Glu Gly His Ser Ile Asn Thr Arg Glu Asn Lys Tyr Ile Pro Pro Gly
485 490 495

Gln Arg Asn Arg Glu Val Ile Ser Trp Gly Ser Gly Arg Gln Asn Ser
500 505 510

Pro Arg Met Gly Gln Pro Gly Ser Gly Ser Met Pro Ser Arg Ser Thr
515 520 525

Ser His Thr Ser Asp Phe Asn Pro Asn Ser Gly Ser Asp Gln Arg Val
530 535 540

Val Asn Gly Gly Val Pro Trp Pro Ser Pro Cys Pro Ser Pro Ser Ser
545 550 555 560

Arg Pro Pro Ser Arg Tyr Gln Ser Gly Pro Asn Ser Leu Pro Pro Arg
565 570 575

Ala	Ala	Thr	Pro	Thr	Arg	Pro	Pro	Ser	Arg	Pro	Pro	Ser	Arg	Pro	Ser	580	585	590	
Arg	Pro	Pro	Ser	His	Pro	Ser	Ala	His	Gly	Ser	Pro	Ala	Pro	Val	Ser	595	600	605	
Thr	Met	Pro	Lys	Arg	Met	Ser	Ser	Glu	Gly	Pro	Pro	Arg	Met	Ser	Pro	610	615	620	
Lys	Ala	Gln	Arg	His	Pro	Arg	Asn	His	Arg	Val	Ser	Ala	Gly	Arg	Gly	625	630	635	640
Ser	Ile	Ser	Ser	Gly	Leu	Glu	Phe	Val	Ser	His	Asn	Pro	Pro	Ser	Glu	645	650	655	
Ala	Ala	Thr	Pro	Pro	Val	Ala	Arg	Thr	Ser	Pro	Ser	Gly	Gly	Thr	Trp	660	665	670	
Ser	Ser	Val	Val	Ser	Gly	Val	Pro	Arg	Leu	Ser	Pro	Lys	Thr	His	Arg	675	680	685	
Pro	Arg	Ser	Pro	Arg	Gln	Asn	Ser	Ile	Gly	Asn	Thr	Pro	Ser	Gly	Pro	690	695	700	
Val	Leu	Ala	Ser	Pro	Gln	Ala	Gly	Ile	Ile	Pro	Thr	Glu	Ala	Val	Ala	705	710	715	720
Met	Pro	Ile	Pro	Ala	Ala	Ser	Pro	Thr	Pro	Ala	Ser	Pro	Ala	Ser	Asn	725	730	735	
Arg	Ala	Val	Thr	Pro	Ser	Ser	Glu	Ala	Lys	Asp	Ser	Arg	Leu	Gln	Asp	740	745	750	
Gln	Arg	Gln	Asn	Ser	Pro	Ala	Gly	Asn	Lys	Glu	Asn	Ile	Lys	Pro	Asn	755	760	765	
Glu	Thr	Ser	Pro	Ser	Phe	Ser	Lys	Ala	Glu	Asn	Lys	Gly	Ile	Ser	Pro	770	775	780	
Val	Val	Ser	Glu	His	Arg	Lys	Gln	Ile	Asp	Asp	Leu	Lys	Lys	Phe	Lys	785	790	795	800
Asn	Asp	Phe	Arg	Leu	Gln	Pro	Ser	Ser	Thr	Ser	Glu	Ser	Met	Asp	Gln	805	810	815	
Leu	Leu	Asn	Lys	Asn	Arg	Glu	Gly	Glu	Lys	Ser	Arg	Asp	Leu	Ile	Lys	820	825	830	
Asp	Lys	Ile	Glu	Pro	Ser	Ala	Lys	Asp	Ser	Phe	Ile	Glu	Asn	Ser	Ser	835	840	845	
Ser	Asn	Cys	Thr	Ser	Gly	Ser	Ser	Lys	Pro	Asn	Ser	Pro	Ser	Ile	Ser	850	855	860	

Pro Ser Ile Leu Ser Asn Thr Glu His Lys Arg Gly Pro Glu Val Thr
 865 870 875 880
 Ser Gln Gly Val Gln Thr Ser Ser Pro Ala Cys Lys Gln Glu Lys Asp
 885 890 895
 Asp Lys Glu Glu Lys Lys Asp Ala Ala Glu Gln Val Arg Lys Ser Thr
 900 905 910
 Leu Asn Pro Asn Ala Lys Glu Phe Asn Pro Arg Ser Phe Ser Gln Pro
 915 920 925
 Lys Pro Ser Thr Thr Pro Thr Ser Pro Arg Pro Gln Ala Gln Pro Ser
 930 935 940
 Pro Ser Met Val Gly His Gln Gln Pro Thr Pro Val Tyr Thr Gln Pro
 945 950 955 960
 Val Cys Phe Ala Pro Asn Met Met Tyr Pro Val Pro Val Ser Pro Gly
 965 970 975
 Val Gln Pro Leu Tyr Pro Ile Pro Met Thr Pro Met Pro Val Asn Gln
 980 985 990
 Ala Lys Thr Tyr Arg Ala Val Pro Asn Met Pro Gln Gln Arg Gln Asp
 995 1000 1005
 Gln His His Gln Ser Ala Met Met His Pro Ala Ser Ala Ala Gly Pro
 1010 1015 1020
 Pro Ile Ala Ala Thr Pro Pro Ala Tyr Ser Thr Gln Tyr Val Ala Tyr
 1025 1030 1035 1040
 Ser Pro Gln Gln Phe Pro Asn Gln Pro Leu Val Gln His Val Pro His
 1045 1050 1055
 Tyr Gln Ser Gln His Pro His Val Tyr Ser Pro Val Ile Gln Gly Asn
 1060 1065 1070
 Ala Arg Met Met Ala Pro Pro Thr His Ala Gln Pro Gly Leu Val Ser
 1075 1080 1085
 Ser Ser Ala Thr Gln Tyr Gly Ala His Glu Gln Thr His Ala Met Tyr
 1090 1095 1100
 Ala Cys Pro Lys Leu Pro Tyr Asn Lys Glu Thr Ser Pro Ser Phe Tyr
 1105 1110 1115 1120
 Phe Ala Ile Ser Thr Gly Ser Leu Ala Gln Gln Tyr Ala His Pro Asn
 1125 1130 1135
 Ala Thr Leu His Pro His Thr Pro His Pro Gln Pro Ser Ala Thr Pro
 1140 1145 1150


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Thr Gly Gln Gln Gln Ser Gln His Gly Gly Ser His Pro Ala Pro Ser
1155                      1160                      1165

Pro Val Gln His His Gln His Gln Ala Ala Gln Ala Leu His Leu Ala
1170                      1175                      1180

Ser Pro Gln Gln Gln Ser Ala Ile Tyr His Ala Gly Leu Ala Pro Thr
1185                      1190                      1195                      1200

Pro Pro Ser Met Thr Pro Ala Ser Asn Thr Gln Ser Pro Gln Asn Ser
1205                      1210                      1215

Phe Pro Ala Ala Gln Gln Thr Val Phe Thr Ile His Pro Ser His Val
1220                      1225                      1230

Gln Pro Ala Tyr Thr Asn Pro Pro His Met Ala His Val Pro Gln Ala
1235                      1240                      1245

His Val Gln Ser Gly Met Val Pro Ser His Pro Thr Ala His Ala Pro
1250                      1255                      1260

Met Met Leu Met Thr Thr Gln Pro Pro Gly Gly Pro Gln Ala Ala Leu
1265                      1270                      1275                      1280

Ala Gln Ser Ala Leu Gln Pro Ile Pro Val Ser Thr Thr Ala His Phe
1285                      1290                      1295

Pro Tyr Met Thr His Pro Ser Val Gln Ala His His Gln Gln Gln Leu
1300                      1305                      1310

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(2) INFORMATION FOR SEQ ID NO:4:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 3798 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: both
- (D) TOPOLOGY: both

(ix) FEATURE:

- (A) NAME/KEY: CDS
- (B) LOCATION: 50..3457

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:4:

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GGCACGAGGT CCCC GCCCGG CGTGCGAGCC GGTGTATGGG CCGCTCACC ATG TCG
                                         Met Ser
                                         1

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CTG AAG CCG CAG CCG CAG CCG CCC GCG CCC GCC ACT GGC CGC AAG CCC Leu Lys Pro Gln Pro Gln Pro Pro Ala Pro Ala Thr Gly Arg Lys Pro 5 10 15	103
GGC GGC GGC CTG CTC TCG TCG CCC GGC GCC GCG CCG GCC TCG GCC GCG Gly Gly Gly Leu Leu Ser Ser Pro Gly Ala Ala Pro Ala Ser Ala Ala 20 25 30	151
GTG ACC TCG GCT TCC GTG GTG CCG GCC CCG GCC GCG CCG GTG GCG TCT Val Thr Ser Ala Ser Val Val Pro Ala Pro Ala Ala Pro Val Ala Ser 35 40 45 50	199
TCC TCG GCG GCC GCG GGC GGC GGG CGT CCC GGC CTG GGC AGA GGT CGG Ser Ser Ala Ala Ala Gly Gly Gly Arg Pro Gly Leu Gly Arg Gly Arg 55 60 65	247
AAC AGT AGC AAA GGA CTG CCT CAG CCT ACG ATT TCT TTT GAT GGA ATC Asn Ser Ser Lys Gly Leu Pro Gln Pro Thr Ile Ser Phe Asp Gly Ile 70 75 80	295
TAT GCA AAC GTG AGG ATG GTT CAT ATA CTT ACG TCA GTT GTT GGA TCG Tyr Ala Asn Val Arg Met Val His Ile Leu Thr Ser Val Val Gly Ser 85 90 95	343
AAA TGT GAA GTA CAA GTG AAA AAC GGA GGC ATA TAT GAA GGA GTT TTT Lys Cys Glu Val Gln Val Lys Asn Gly Gly Ile Tyr Glu Gly Val Phe 100 105 110	391
AAA ACA TAC AGT CCT AAG TGT GAC TTG GTA CTT GAT GCT GCA CAT GAG Lys Thr Tyr Ser Pro Lys Cys Asp Leu Val Leu Asp Ala Ala His Glu 115 120 125 130	439
AAA AGT ACA GAA TCC AGT TCG GGG CCA AAA CGT GAA GAA ATA ATG GAG Lys Ser Thr Glu Ser Ser Ser Gly Pro Lys Arg Glu Glu Ile Met Glu 135 140 145	487
AGT GTT TTG TTC AAA TGC TCA GAC TTC GTT GTG GTA CAG TTT AAA GAT Ser Val Leu Phe Lys Cys Ser Asp Phe Val Val Val Gln Phe Lys Asp 150 155 160	535
ACA GAC TCC AGT TAT GCA CGG AGA GAT GCT TTT ACT GAC TCT GCT CTC Thr Asp Ser Ser Tyr Ala Arg Arg Asp Ala Phe Thr Asp Ser Ala Leu 165 170 175	583
AGC GCA AAG GTG AAT GGT GAG CAC AAG GAG AAG GAC CTG GAG CCC TGG Ser Ala Lys Val Asn Gly Glu His Lys Glu Lys Asp Leu Glu Pro Trp 180 185 190	631
GAT GCA GGG GAG CTC ACG GCC AGC GAG GAG CTG GAG CTG GAG AAT GAT Asp Ala Gly Glu Leu Thr Ala Ser Glu Glu Leu Glu Leu Glu Asn Asp 195 200 205 210	679
GTG TCT AAT GGA TGG GAC CCC AAT GAC ATG TTT CGA TAT AAT GAA GAG Val Ser Asn Gly Trp Asp Pro Asn Asp Met Phe Arg Tyr Asn Glu Glu 215 220 225	727

AAT TAT GGT GTG GTG TCC ACA TAT GAT AGC AGT TTA TCT TCA TAT ACG	775
Asn Tyr Gly Val Val Ser Thr Tyr Asp Ser Ser Leu Ser Ser Tyr Thr	
230 235 240	
GTT CCT TTA GAA AGG GAC AAC TCA GAA GAA TTT CTT AAA CGG GAG GCA	823
Val Pro Leu Glu Arg Asp Asn Ser Glu Glu Phe Leu Lys Arg Glu Ala	
245 250 255	
AGG GCA AAC CAG TTA GCA GAA GAA ATT GAA TCC AGT GCT CAG TAC AAA	871
Arg Ala Asn Gln Leu Ala Glu Glu Ile Glu Ser Ser Ala Gln Tyr Lys	
260 265 270	
GCT CGT GTC GCC CTT GAG AAT GAT GAC CGG AGT GAG GAA GAA AAA TAC	919
Ala Arg Val Ala Leu Glu Asn Asp Asp Arg Ser Glu Glu Glu Lys Tyr	
275 280 285 290	
ACA GCA GTC CAG AGA AAC TGC AGT GAC CGG GAG GGG CAT GGC CCC AAC	967
Thr Ala Val Gln Arg Asn Cys Ser Asp Arg Glu Gly His Gly Pro Asn	
295 300 305	
ACT AGG GAC AAT AAA TAT ATT CCT CCT GGA CAA AGA AAC AGA GAA GTC	1015
Thr Arg Asp Asn Lys Tyr Ile Pro Pro Gly Gln Arg Asn Arg Glu Val	
310 315 320	
CTA TCC TGG GGA AGT GGG AGA CAG AGC TCA CCA CGG ATG GGC CAG CCT	1063
Leu Ser Trp Gly Ser Gly Arg Gln Ser Ser Pro Arg Met Gly Gln Pro	
325 330 335	
GGG CCA GGC TCC ATG CCG TCA AGA GCT GCT TCT CAC ACT TCA GAT TTC	1111
Gly Pro Gly Ser Met Pro Ser Arg Ala Ala Ser His Thr Ser Asp Phe	
340 345 350	
AAC CCG AAC GCT GGC TCA GAC CAA AGA GTA GTT AAT GGA GGT GTT CCC	1159
Asn Pro Asn Ala Gly Ser Asp Gln Arg Val Val Asn Gly Gly Val Pro	
355 360 365 370	
TGG CCA TCG CCT TGC CCA TCT CAT TCC TCT CGC CCA CCT TCT CGC TAC	1207
Trp Pro Ser Pro Cys Pro Ser His Ser Ser Arg Pro Pro Ser Arg Tyr	
375 380 385	
CAG TCA GGT CCC AAC TCT CTT CCA CCT CGG GCA GCC ACC CAT ACA CGG	1255
Gln Ser Gly Pro Asn Ser Leu Pro Pro Arg Ala Ala Thr His Thr Arg	
390 395 400	
CCG CCC TCC AGG CCC CCC TCG AGG CCA TCC AGA CCC CCG TCT CAC CCC	1303
Pro Pro Ser Arg Pro Pro Ser Arg Pro Ser Arg Pro Pro Ser His Pro	
405 410 415	
TCT GCT CAT GGT TCT CCA GCT CCT GTC TCT ACT ATG CCT AAA CGC ATG	1351
Ser Ala His Gly Ser Pro Ala Pro Val Ser Thr Met Pro Lys Arg Met	
420 425 430	
TCT TCA GAA GGA CCC CCA AGG ATG TCT CCA AAG GCA CAG CGC CAC CCT	1399
Ser Ser Glu Gly Pro Pro Arg Met Ser Pro Lys Ala Gln Arg His Pro	
435 440 445 450	

CGG	AAT	CAC	AGA	GTC	TCT	GCT	GGG	AGA	GGC	TCC	ATG	TCT	AGT	GGC	CTA	1447
Arg	Asn	His	Arg	Val	Ser	Ala	Gly	Arg	Gly	Ser	Met	Ser	Ser	Gly	Leu	
				455					460					465		
GAA	TTT	GTA	TCC	CAC	AAT	CCC	CCA	AGT	GAA	GCA	GCT	GCT	CCT	CCA	GTG	1495
Glu	Phe	Val	Ser	His	Asn	Pro	Pro	Ser	Glu	Ala	Ala	Ala	Pro	Pro	Val	
			470					475					480			
GCA	AGG	ACC	AGT	CCT	GCA	GGG	GGA	ACG	TGG	TCC	TCA	GTG	GTC	AGT	GGG	1543
Ala	Arg	Thr	Ser	Pro	Ala	Gly	Gly	Thr	Trp	Ser	Ser	Val	Val	Ser	Gly	
		485					490					495				
GTT	CCA	AGG	TTA	TCT	CCC	AAA	ACT	CAC	AGA	CCC	AGG	TCT	CCC	AGG	CAG	1591
Val	Pro	Arg	Leu	Ser	Pro	Lys	Thr	His	Arg	Pro	Arg	Ser	Pro	Arg	Gln	
	500					505					510					
AGC	AGC	ATT	GGA	AAC	TCT	CCC	AGC	GGG	CCT	GTG	CTT	GCT	TCT	CCC	CAA	1639
Ser	Ser	Ile	Gly	Asn	Ser	Pro	Ser	Gly	Pro	Val	Leu	Ala	Ser	Pro	Gln	
515				520						525					530	
GCT	GGC	ATC	ATC	CCT	GCA	GAA	GCC	GTT	TCC	ATG	CCT	GTT	CCC	GCC	GCA	1687
Ala	Gly	Ile	Ile	Pro	Ala	Glu	Ala	Val	Ser	Met	Pro	Val	Pro	Ala	Ala	
				535					540					545		
TCT	CCG	ACT	CCT	GCC	AGC	CCT	GCA	TCC	AAC	AGA	GCA	CTG	ACC	CCA	TCT	1735
Ser	Pro	Thr	Pro	Ala	Ser	Pro	Ala	Ser	Asn	Arg	Ala	Leu	Thr	Pro	Ser	
			550					555					560			
ATT	GAG	GCA	AAA	GAT	TCC	AGG	CTT	CAA	GAT	CAG	AGG	CAG	AAC	TCT	CCT	1783
Ile	Glu	Ala	Lys	Asp	Ser	Arg	Leu	Gln	Asp	Gln	Arg	Gln	Asn	Ser	Pro	
		565					570					575				
GCA	GGG	AGT	AAA	GAA	AAT	GTT	AAA	GCA	AGT	GAA	ACA	TCA	CCT	AGC	TTT	1831
Ala	Gly	Ser	Lys	Glu	Asn	Val	Lys	Ala	Ser	Glu	Thr	Ser	Pro	Ser	Phe	
	580					585					590					
TCA	AAA	GCT	GAC	AAC	AAA	GGT	ATG	TCA	CCA	GTT	GTT	TCT	GAA	CAC	AGA	1879
Ser	Lys	Ala	Asp	Asn	Lys	Gly	Met	Ser	Pro	Val	Val	Ser	Glu	His	Arg	
595				600						605					610	
AAA	CAG	ATT	GAT	GAC	TTA	AAG	AAG	TTT	AAG	AAT	GAT	TTT	AGG	TTA	CAG	1927
Lys	Gln	Ile	Asp	Asp	Leu	Lys	Lys	Phe	Lys	Asn	Asp	Phe	Arg	Leu	Gln	
			615						620					625		
CCA	AGC	TCT	ACA	TCT	GAA	TCT	ATG	GAT	CAA	CTA	CTA	AGC	AAA	AAT	AGA	1975
Pro	Ser	Ser	Thr	Ser	Glu	Ser	Met	Asp	Gln	Leu	Leu	Ser	Lys	Asn	Arg	
			630					635					640			
GAA	GGA	GAA	AAG	TCA	CGA	GAT	TTG	ATT	AAA	GAT	AAA	ACG	GAA	GCA	AGT	2023
Glu	Gly	Glu	Lys	Ser	Arg	Asp	Leu	Ile	Lys	Asp	Lys	Thr	Glu	Ala	Ser	
		645					650					655				
GCT	AAG	GAT	AGT	TTC	ATT	GAC	AGC	AGC	AGC	AGC	AGC	AGC	AAC	TGT	ACC	2071
Ala	Lys	Asp	Ser	Phe	Ile	Asp	Ser	Ser	Ser	Ser	Ser	Ser	Asn	Cys	Thr	
	660					665						670				

AGT GGC AGC AGC AAG ACC AAC AGC CCT AGC ATC TCC CCT TCC ATG CTT	2119
Ser Gly Ser Ser Lys Thr Asn Ser Pro Ser Ile Ser Pro Ser Met Leu	
675 680 685 690	
AGT AAT GCA GAG CAC AAG AGG GGG CCT GAG GTC ACA TCC CAA GGG GTG	2167
Ser Asn Ala Glu His Lys Arg Gly Pro Glu Val Thr Ser Gln Gly Val	
695 700 705	
CAG ACT TCC AGC CCA GCC TGC AAA CAA GAG AAG GAT GAC AGA GAA GAG	2215
Gln Thr Ser Ser Pro Ala Cys Lys Gln Glu Lys Asp Asp Arg Glu Glu	
710 715 720	
AAG AAA GAC ACA ACA GAG CAG GTT AGG AAA TCG ACA TTG AAT CCC AAT	2263
Lys Lys Asp Thr Thr Glu Gln Val Arg Lys Ser Thr Leu Asn Pro Asn	
725 730 735	
GCA AAG GAG TTC AAC CCT CGT TCT TTC TCT CAG CCA AAG CCT TCT ACT	2311
Ala Lys Glu Phe Asn Pro Arg Ser Phe Ser Gln Pro Lys Pro Ser Thr	
740 745 750	
ACC CCA ACG TCA CCT CGG CCT CAA GCA CAA CCC AGC CCA TCT ATG GTG	2359
Thr Pro Thr Ser Pro Arg Pro Gln Ala Gln Pro Ser Pro Ser Met Val	
755 760 765 770	
GGT CAT CAG CAG CCA GCT CCA GTG TAC ACT CAG CCT GTG TGC TTC GCA	2407
Gly His Gln Gln Pro Ala Pro Val Tyr Thr Gln Pro Val Cys Phe Ala	
775 780 785	
CCC AAT ATG ATG TAT CCC GTC CCA GTG AGC CCG GGC GTA CAA CCT TTA	2455
Pro Asn Met Met Tyr Pro Val Pro Val Ser Pro Gly Val Gln Pro Leu	
790 795 800	
TAC CCA ATA CCT ATG ACG CCC ATG CCT GTG AAC CAA GCC AAG ACA TAT	2503
Tyr Pro Ile Pro Met Thr Pro Met Pro Val Asn Gln Ala Lys Thr Tyr	
805 810 815	
AGA GCA GGT AAA GTA CCA AAT ATG CCC CAA CAG CGA CAA GAC CAA CAT	2551
Arg Ala Gly Lys Val Pro Asn Met Pro Gln Gln Arg Gln Asp Gln His	
820 825 830	
CAT CAA AGC ACC ATG ATG CAC CCA GCC TCC GCG GCA GGG CCA CCC ATC	2599
His Gln Ser Thr Met Met His Pro Ala Ser Ala Ala Gly Pro Pro Ile	
835 840 845 850	
GTA GCC ACC CCG CCC GCT TAC TCC ACT CAG TAC GTT GCC TAC AGC CCT	2647
Val Ala Thr Pro Pro Ala Tyr Ser Thr Gln Tyr Val Ala Tyr Ser Pro	
855 860 865	
CAG CAG TTT CCC AAT CAG CCT TTG GTC CAG CAT GTG CCG CAT TAT CAG	2695
Gln Gln Phe Pro Asn Gln Pro Leu Val Gln His Val Pro His Tyr Gln	
870 875 880	
TCT CAG CAT CCT CAT GTG TAC AGT CCT GTC ATA CAA GGT AAT GCC AGG	2743
Ser Gln His Pro His Val Tyr Ser Pro Val Ile Gln Gly Asn Ala Arg	
885 890 895	

ATG	ATG	GCA	CCA	CCA	GCA	CAT	GCT	CAG	CCT	GGT	TTA	GTG	TCT	TCT	TCA	2791
Met	Met	Ala	Pro	Pro	Ala	His	Ala	Gln	Pro	Gly	Leu	Val	Ser	Ser	Ser	
	900					905					910					
GCT	GCT	CAG	TTC	GGG	GCT	CAC	GAG	CAG	ACG	CAC	GCC	ATG	TAT	GCA	TGT	2839
Ala	Ala	Gln	Phe	Gly	Ala	His	Glu	Gln	Thr	His	Ala	Met	Tyr	Ala	Cys	
915					920					925					930	
CCC	AAA	TTA	CCA	TAC	AAC	AAG	GAG	ACA	AGC	CCT	TCT	TTC	TAC	TTT	GCC	2887
Pro	Lys	Leu	Pro	Tyr	Asn	Lys	Glu	Thr	Ser	Pro	Ser	Phe	Tyr	Phe	Ala	
				935					940					945		
ATT	TCC	ACC	GGC	TCC	CTC	GCT	CAG	CAG	TAT	GCA	CAT	CCT	AAT	GCC	GCC	2935
Ile	Ser	Thr	Gly	Ser	Leu	Ala	Gln	Gln	Tyr	Ala	His	Pro	Asn	Ala	Ala	
			950					955					960			
CTG	CAT	CCA	CAT	ACT	CCC	CAT	CCT	CAG	CCT	TCG	GCC	ACT	CCC	ACC	GGA	2983
Leu	His	Pro	His	Thr	Pro	His	Pro	Gln	Pro	Ser	Ala	Thr	Pro	Thr	Gly	
	965						970					975				
CAG	CAG	CAA	AGC	CAG	CAT	GGT	GGA	AGT	CAC	CCT	GCA	CCC	AGT	CCT	GTT	3031
Gln	Gln	Gln	Ser	Gln	His	Gly	Gly	Ser	His	Pro	Ala	Pro	Ser	Pro	Val	
	980					985					990					
CAG	CAC	CAT	CAG	CAC	CAG	GCT	GCC	CAG	GCT	CTT	CAT	CTG	GCC	AGT	CCA	3079
Gln	His	His	Gln	His	Gln	Ala	Ala	Gln	Ala	Leu	His	Leu	Ala	Ser	Pro	
995					1000					1005					1010	
CAG	CAG	CAG	TCG	GCC	ATT	TAT	CAT	GCG	GGG	CTG	GCA	CCA	ACA	CCA	CCT	3127
Gln	Gln	Gln	Ser	Ala	Ile	Tyr	His	Ala	Gly	Leu	Ala	Pro	Thr	Pro	Pro	
				1015					1020					1025		
TCC	ATG	ACA	CCT	GCC	TCT	AAT	ACA	CAG	TCT	CCA	CAG	AGC	AGT	TTC	CCA	3175
Ser	Met	Thr	Pro	Ala	Ser	Asn	Thr	Gln	Ser	Pro	Gln	Ser	Ser	Phe	Pro	
			1030					1035					1040			
GCA	GCA	CAA	CAG	ACA	GTC	TTC	ACC	ATC	CAC	CCT	TCT	CAT	GTT	CAG	CCG	3223
Ala	Ala	Gln	Gln	Thr	Val	Phe	Thr	Ile	His	Pro	Ser	His	Val	Gln	Pro	
	1045						1050					1055				
GCA	TAC	ACC	ACC	CCA	CCC	CAC	ATG	GCC	CAC	GTA	CCT	CAG	GCT	CAT	GTA	3271
Ala	Tyr	Thr	Thr	Pro	Pro	His	Met	Ala	His	Val	Pro	Gln	Ala	His	Val	
	1060					1065				1070						
CAG	TCA	GGA	ATG	GTT	CCT	TCT	CAT	CCA	ACT	GCC	CAT	GCG	CCA	ATG	ATG	3319
Gln	Ser	Gly	Met	Val	Pro	Ser	His	Pro	Thr	Ala	His	Ala	Pro	Met	Met	
1075					1080					1085				1090		
CTA	ATG	ACG	ACA	CAG	CCA	CCC	GGT	CCC	AAG	GCC	GCC	CTC	GCT	CAA	AGT	3367
Leu	Met	Thr	Thr	Gln	Pro	Pro	Gly	Pro	Lys	Ala	Ala	Leu	Ala	Gln	Ser	
				1095					1100					1105		
GCA	CTA	CAG	CCC	ATT	CCA	GTT	TCG	ACA	ACA	GCG	CAT	TTC	CCT	TAT	ATG	3415
Ala	Leu	Gln	Pro	Ile	Pro	Val	Ser	Thr	Thr	Ala	His	Phe	Pro	Tyr	Met	
			1110					1115					1120			

ACG CAC CCT TCA GTA CAA GCC CAC CAC CAA CAG CAG TTG TAAGGCTGCC 3464
 Thr His Pro Ser Val Gln Ala His His Gln Gln Gln Leu
 1125 1130 1135

TTGGAGGAAC CGAAAGGCCA AATCCCTTCT TCCCTTCTCT GCTTCTGCCA ACCGGAAGCA 3524

CAGAAAATA GAACTTCATT GATTTTGTTT TTTAAAGAT ACACTGATTT AACATCTGAT 3584

AGGAATGCTA ACAGCTCACT TGCAGTGGAG GATCTTTTGG ACCGAGTAGA GGCATGTAGG 3644

GACTTGTGGC TGTTCATAA TTCCATGTGC TGTTCAGGG TCCTGCAAGT ACCCAGCTCT 3704

GCTTGCTGAA ACTGGAAGTT ATTTATTTTT TAATGGCCCT TGAGAGTCAT GAACACATCA 3764

GCTAGCAACA GAAGTAACAA GAGTGATTCT TGCT 3798

(2) INFORMATION FOR SEQ ID NO:5:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 1135 amino acids
 (B) TYPE: amino acid
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:5:

Met Ser Leu Lys Pro Gln Pro Gln Pro Pro Ala Pro Ala Thr Gly Arg
 1 5 10 15

Lys Pro Gly Gly Gly Leu Leu Ser Ser Pro Gly Ala Ala Pro Ala Ser
 20 25 30

Ala Ala Val Thr Ser Ala Ser Val Val Pro Ala Pro Ala Ala Pro Val
 35 40 45

Ala Ser Ser Ser Ala Ala Ala Gly Gly Gly Arg Pro Gly Leu Gly Arg
 50 55 60

Gly Arg Asn Ser Ser Lys Gly Leu Pro Gln Pro Thr Ile Ser Phe Asp
 65 70 75 80

Gly Ile Tyr Ala Asn Val Arg Met Val His Ile Leu Thr Ser Val Val
 85 90 95

Gly Ser Lys Cys Glu Val Gln Val Lys Asn Gly Gly Ile Tyr Glu Gly
 100 105 110

Val Phe Lys Thr Tyr Ser Pro Lys Cys Asp Leu Val Leu Asp Ala Ala
 115 120 125

His Glu Lys Ser Thr Glu Ser Ser Ser Gly Pro Lys Arg Glu Glu Ile
 130 135 140

Met	Glu	Ser	Val	Leu	Phe	Lys	Cys	Ser	Asp	Phe	Val	Val	Val	Gln	Phe	145	150	155	160
Lys	Asp	Thr	Asp	Ser	Ser	Tyr	Ala	Arg	Arg	Asp	Ala	Phe	Thr	Asp	Ser	165	170	175	
Ala	Leu	Ser	Ala	Lys	Val	Asn	Gly	Glu	His	Lys	Glu	Lys	Asp	Leu	Glu	180	185	190	
Pro	Trp	Asp	Ala	Gly	Glu	Leu	Thr	Ala	Ser	Glu	Glu	Leu	Glu	Leu	Glu	195	200	205	
Asn	Asp	Val	Ser	Asn	Gly	Trp	Asp	Pro	Asn	Asp	Met	Phe	Arg	Tyr	Asn	210	215	220	
Glu	Glu	Asn	Tyr	Gly	Val	Val	Ser	Thr	Tyr	Asp	Ser	Ser	Leu	Ser	Ser	225	230	235	240
Tyr	Thr	Val	Pro	Leu	Glu	Arg	Asp	Asn	Ser	Glu	Glu	Phe	Leu	Lys	Arg	245	250	255	
Glu	Ala	Arg	Ala	Asn	Gln	Leu	Ala	Glu	Glu	Ile	Glu	Ser	Ser	Ala	Gln	260	265	270	
Tyr	Lys	Ala	Arg	Val	Ala	Leu	Glu	Asn	Asp	Asp	Arg	Ser	Glu	Glu	Glu	275	280	285	
Lys	Tyr	Thr	Ala	Val	Gln	Arg	Asn	Cys	Ser	Asp	Arg	Glu	Gly	His	Gly	290	295	300	
Pro	Asn	Thr	Arg	Asp	Asn	Lys	Tyr	Ile	Pro	Pro	Gly	Gln	Arg	Asn	Arg	305	310	315	320
Glu	Val	Leu	Ser	Trp	Gly	Ser	Gly	Arg	Gln	Ser	Ser	Pro	Arg	Met	Gly	325	330	335	
Gln	Pro	Gly	Pro	Gly	Ser	Met	Pro	Ser	Arg	Ala	Ala	Ser	His	Thr	Ser	340	345	350	
Asp	Phe	Asn	Pro	Asn	Ala	Gly	Ser	Asp	Gln	Arg	Val	Val	Asn	Gly	Gly	355	360	365	
Val	Pro	Trp	Pro	Ser	Pro	Cys	Pro	Ser	His	Ser	Ser	Arg	Pro	Pro	Ser	370	375	380	
Arg	Tyr	Gln	Ser	Gly	Pro	Asn	Ser	Leu	Pro	Pro	Arg	Ala	Ala	Thr	His	385	390	395	400
Thr	Arg	Pro	Pro	Ser	Arg	Pro	Pro	Ser	Arg	Pro	Ser	Arg	Pro	Pro	Ser	405	410	415	
His	Pro	Ser	Ala	His	Gly	Ser	Pro	Ala	Pro	Val	Ser	Thr	Met	Pro	Lys	420	425	430	

Arg Met Ser Ser Glu Gly Pro Pro Arg Met Ser Pro Lys Ala Gln Arg
 435 440 445
 His Pro Arg Asn His Arg Val Ser Ala Gly Arg Gly Ser Met Ser Ser
 450 455 460
 Gly Leu Glu Phe Val Ser His Asn Pro Pro Ser Glu Ala Ala Ala Pro
 465 470 475 480
 Pro Val Ala Arg Thr Ser Pro Ala Gly Gly Thr Trp Ser Ser Val Val
 485 490 495
 Ser Gly Val Pro Arg Leu Ser Pro Lys Thr His Arg Pro Arg Ser Pro
 500 505 510
 Arg Gln Ser Ser Ile Gly Asn Ser Pro Ser Gly Pro Val Leu Ala Ser
 515 520 525
 Pro Gln Ala Gly Ile Ile Pro Ala Glu Ala Val Ser Met Pro Val Pro
 530 535 540
 Ala Ala Ser Pro Thr Pro Ala Ser Pro Ala Ser Asn Arg Ala Leu Thr
 545 550 555 560
 Pro Ser Ile Glu Ala Lys Asp Ser Arg Leu Gln Asp Gln Arg Gln Asn
 565 570 575
 Ser Pro Ala Gly Ser Lys Glu Asn Val Lys Ala Ser Glu Thr Ser Pro
 580 585 590
 Ser Phe Ser Lys Ala Asp Asn Lys Gly Met Ser Pro Val Val Ser Glu
 595 600 605
 His Arg Lys Gln Ile Asp Asp Leu Lys Lys Phe Lys Asn Asp Phe Arg
 610 615 620
 Leu Gln Pro Ser Ser Thr Ser Glu Ser Met Asp Gln Leu Leu Ser Lys
 625 630 635 640
 Asn Arg Glu Gly Glu Lys Ser Arg Asp Leu Ile Lys Asp Lys Thr Glu
 645 650 655
 Ala Ser Ala Lys Asp Ser Phe Ile Asp Ser Ser Ser Ser Ser Ser Asn
 660 665 670
 Cys Thr Ser Gly Ser Ser Lys Thr Asn Ser Pro Ser Ile Ser Pro Ser
 675 680 685
 Met Leu Ser Asn Ala Glu His Lys Arg Gly Pro Glu Val Thr Ser Gln
 690 695 700
 Gly Val Gln Thr Ser Ser Pro Ala Cys Lys Gln Glu Lys Asp Asp Arg
 705 710 715 720

Glu Glu Lys Lys Asp Thr Thr Glu Gln Val Arg Lys Ser Thr Leu Asn
 725 730 735
 Pro Asn Ala Lys Glu Phe Asn Pro Arg Ser Phe Ser Gln Pro Lys Pro
 740 745 750
 Ser Thr Thr Pro Thr Ser Pro Arg Pro Gln Ala Gln Pro Ser Pro Ser
 755 760 765
 Met Val Gly His Gln Gln Pro Ala Pro Val Tyr Thr Gln Pro Val Cys
 770 775 780
 Phe Ala Pro Asn Met Met Tyr Pro Val Pro Val Ser Pro Gly Val Gln
 785 790 795 800
 Pro Leu Tyr Pro Ile Pro Met Thr Pro Met Pro Val Asn Gln Ala Lys
 805 810 815
 Thr Tyr Arg Ala Gly Lys Val Pro Asn Met Pro Gln Gln Arg Gln Asp
 820 825 830
 Gln His His Gln Ser Thr Met Met His Pro Ala Ser Ala Ala Gly Pro
 835 840 845
 Pro Ile Val Ala Thr Pro Pro Ala Tyr Ser Thr Gln Tyr Val Ala Tyr
 850 855 860
 Ser Pro Gln Gln Phe Pro Asn Gln Pro Leu Val Gln His Val Pro His
 865 870 875 880
 Tyr Gln Ser Gln His Pro His Val Tyr Ser Pro Val Ile Gln Gly Asn
 885 890 895
 Ala Arg Met Met Ala Pro Pro Ala His Ala Gln Pro Gly Leu Val Ser
 900 905 910
 Ser Ser Ala Ala Gln Phe Gly Ala His Glu Gln Thr His Ala Met Tyr
 915 920 925
 Ala Cys Pro Lys Leu Pro Tyr Asn Lys Glu Thr Ser Pro Ser Phe Tyr
 930 935 940
 Phe Ala Ile Ser Thr Gly Ser Leu Ala Gln Gln Tyr Ala His Pro Asn
 945 950 955 960
 Ala Ala Leu His Pro His Thr Pro His Pro Gln Pro Ser Ala Thr Pro
 965 970 975
 Thr Gly Gln Gln Gln Ser Gln His Gly Gly Ser His Pro Ala Pro Ser
 980 985 990
 Pro Val Gln His His Gln His Gln Ala Ala Gln Ala Leu His Leu Ala
 995 1000 1005

Ser Pro Gln Gln Gln Ser Ala Ile Tyr His Ala Gly Leu Ala Pro Thr
1010 1015 1020

Pro Pro Ser Met Thr Pro Ala Ser Asn Thr Gln Ser Pro Gln Ser Ser
1025 1030 1035 1040

Phe Pro Ala Ala Gln Gln Thr Val Phe Thr Ile His Pro Ser His Val
1045 1050 1055

Gln Pro Ala Tyr Thr Thr Pro Pro His Met Ala His Val Pro Gln Ala
1060 1065 1070

His Val Gln Ser Gly Met Val Pro Ser His Pro Thr Ala His Ala Pro
1075 1080 1085

Met Met Leu Met Thr Thr Gln Pro Pro Gly Pro Lys Ala Ala Leu Ala
1090 1095 1100

Gln Ser Ala Leu Gln Pro Ile Pro Val Ser Thr Thr Ala His Phe Pro
1105 1110 1115 1120

Tyr Met Thr His Pro Ser Val Gln Ala His His Gln Gln Gln Leu
1125 1130 1135

That which is claimed is:

1. Isolated nucleic acid encoding a mammalian SCA2 polypeptide.
2. Isolated nucleic acid according to claim 1, wherein said nucleic acid comprises DNA.
3. DNA according to claim 2, wherein said DNA is a cDNA.
4. DNA according to claim 2, wherein said DNA encodes at least about 10 contiguous amino acids set forth in SEQ ID NO:3, or SEQ ID NO:5.
5. DNA according to claim 2, wherein said DNA hybridizes under high stringency conditions to the SCA2 coding portion of nucleotides 1 - 516 of SEQ ID NO:1 or nucleotides 163-4098 of SEQ ID NO:2 , or nucleotides 50-3454 of SEQ ID NO:4.
6. DNA according to claim 2, wherein said DNA has substantially the same nucleotide sequence as the SCA2 coding portion set forth in SEQ ID NO:2, or SEQ ID NO:4.
7. A vector comprising DNA according to claim 2.
8. A host cell containing a vector according to claim 7, wherein said cell is a procaryotic cell or a eucaryotic cell.
9. A host cell according to claim 8, wherein said cell expresses a functional SCA2 protein.

10. An oligonucleotide comprising at least 15 nucleotides capable of specifically hybridizing with a sequence of nucleic acids of the nucleotide sequence set forth in SEQ ID NO:2, or SEQ ID NO:4.

11. An oligonucleotide according to claim 10, wherein said oligonucleotide is labeled with a detectable marker.

12. A kit for detecting mutations and in chromosome 12 at the SCA2 locus in 12q24.1 comprising at least one oligonucleotide according to claim 10.

13. Isolated mRNA complementary to DNA according to claim 2.

14. An oligonucleotide composition comprising chemical analogues of the nucleic acid of claim 2 operatively linked to a promoter of RNA transcription.

15. An antisense oligonucleotide capable of specifically binding to and inhibiting the translation of mRNA according to claim 13.

16. Isolated SCA2 polypeptide, or fragments thereof, and functional equivalents thereof.

17. Isolated SCA2 polypeptide according to claim 16, wherein said polypeptide comprises substantially the same amino acid sequence as that set forth in SEQ ID NO:3, amino acids 1-165 or amino acids 188-1312 of SEQ ID NO:3, or substantially the same amino acid sequence as that set forth in SEQ ID NO:5.

18. Isolated SCA2 polypeptide according to claim 16, wherein said polypeptide has the same amino acid sequence as that set forth in SEQ ID NO:3, or at least amino acids 1-165 or amino acids 188-1312 of SEQ ID NO:3, or in SEQ ID NO:5.

19. Isolated SCA2 polypeptide according to claim 16, wherein said polypeptide is encoded by a nucleotide sequence that is substantially the same nucleotide sequence as that set forth in SEQ ID NO:2, nucleotides 163-4098 of SEQ ID NO:2, SEQ ID NO:4, or nucleotides 50-3454 of SEQ ID NO:4.

20. Isolated SCA2 polypeptide according to claim 16, wherein said polypeptide is encoded by at least nucleotides 163-4098 set forth in SEQ ID NO:2, or at least nucleotides 50-3454 of SEQ ID NO:4.

21. An SCA2 polypeptide expressed recombinantly in a host cell.

22. An SCA2 polypeptide according to claim 21, wherein said polypeptide is encoded by a nucleotide sequence that is substantially the same as at least nucleotides 163-4098 set forth in SEQ ID NO:2, or at least nucleotides 50-3454 of SEQ ID NO:4.

23. An SCA2 polypeptide according to claim 21, wherein said polypeptide is encoded by at least nucleotides 163-4098 set forth in SEQ ID NO:2, or at least nucleotides 50-3454 of SEQ ID NO:4.

24. An antibody that specifically binds to a determinant on a SCA2 polypeptide according to claim 16, or active fragment thereof.

25. An antibody according to claim 24, wherein said antibody is a monoclonal antibody.

26. An antibody according to claim 24, wherein said antibody is a polyclonal antibody.

27. A composition comprising an amount of the antisense oligonucleotide according to claim 13 effective to modulate expression of a human SCA2 polypeptide and an acceptable hydrophobic carrier capable of passing through a cell membrane.

28. A composition according to claim 27, wherein the oligonucleotide is coupled to a substance which inactivates mRNA.

29. A composition according to claim 28, wherein said substance is a ribozyme.

30. A composition comprising an amount of an antibody according to claim 24 effective to block function of the SCA2 protein or to block interaction of the SCA2 protein with other proteins or ligands.

31. A transgenic nonhuman mammal expressing DNA encoding a SCA2 polypeptide according to claim 2.

32. A transgenic nonhuman mammal according to claim 31, wherein said DNA encoding said polypeptide has been mutated as to be incapable of normal polypeptide activity, and wherein the polypeptide so expressed is not native SCA2 polypeptide.

33. A transgenic nonhuman mammal, the genome of which comprising antisense DNA complementary to DNA encoding a SCA2 polypeptide according to claim 2, wherein said antisense DNA is transcribed into antisense mRNA complementary to mRNA encoding a human SCA2 polypeptide.

34. A transgenic nonhuman mammal according to claim 31, wherein said DNA is operatively linked to an inducible promoter.

35. A transgenic nonhuman mammal according to claim 31, wherein said DNA is operatively linked to tissue specific regulatory elements.

36. A transgenic nonhuman mammal according to claim 31, wherein the transgenic nonhuman mammal is a mouse.

37. A method for identifying nucleic acids encoding a human SCA2 protein, said method comprising:
contacting a sample containing nucleic acids with a probe according to claim 11, wherein said contacting is effected under high stringency hybridization conditions, and identifying compounds which hybridize thereto.

38. A method for identifying compound(s) which bind to a human SCA2 polypeptide, said method comprising contacting cells according to claim 9 with said compound(s) and identifying compounds which bind thereto.

39. A method for detecting the presence of a human SCA2 polypeptide, said method comprising contacting a test sample with an antibody according to claim 24, detecting the presence of an antibody-SCA2 complex, and therefor detecting the presence of a human SCA2 polypeptide in said test sample.

40. Single strand DNA primers for amplification diagnosis of SCA2, wherein said primers comprise a nucleic acid sequence derived from the nucleic acid according to claim 1 set forth as SEQ ID NO:2, or SEQ ID NO:4.

41. A method for diagnosing spinocerebellar Ataxia Type 2, said method comprising:

detecting, in said subject, a genomic or transcribed mRNA sequence having an expanded CAG repeat at a location corresponding to between nucleotides 657 and 724 of SEQ ID NO:2.

42. A method for diagnosing spinocerebellar Ataxia Type 2, said method comprising:

a) contacting nucleic acid obtained from a subject suspected of having SCA2 with primers that amplify at least a nucleic acid fragment of SEQ ID NO:2 containing nucleotides 658-723 of SEQ ID NO:2, under conditions suitable to form a detectable amplification product; and

b) detecting an amplification product containing substantially expanded CAG repeats above normal, whereby said detection indicates that said subject has SCA2.

43. A diagnostic kit comprising at least one oligonucleotide according to claim 10 contained in a packaging material.

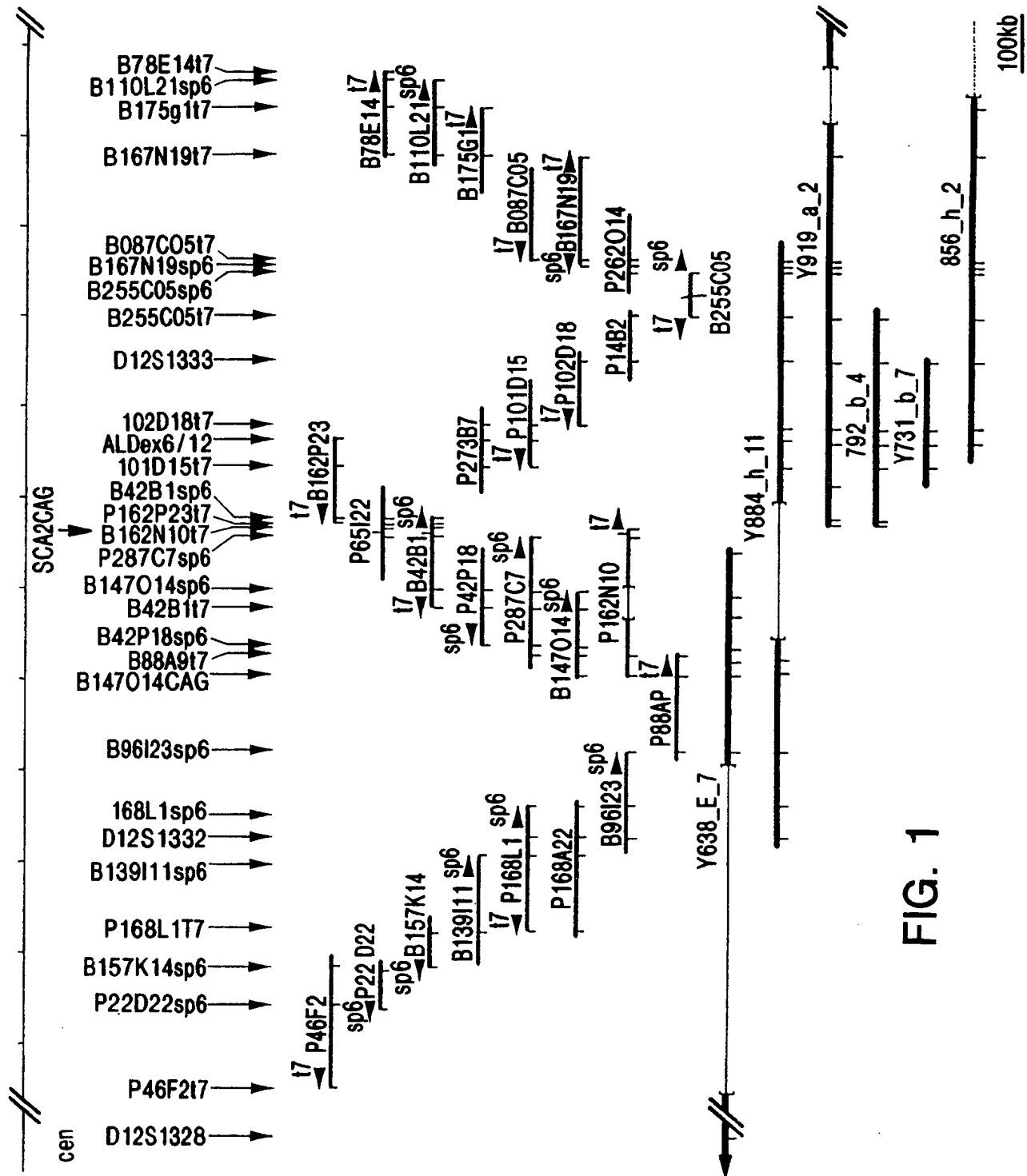


FIG. 1

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1 TTGGTAGCAACGGAAACGGCGGGCGGCGCGTTTCGGCCCGGCTCCCGGCGGCTCCTTGGTG
61 TCGGCGGGCCTCCCCGCCCTTCGTCGTGTCCTTCTCCCCCTCGCCAGCCCGGGCGCCC
121 CTCCGGCCGCGCCAACCCGCGCCTCCCCGCTCGGGCGCCCGTGCGTCCCGCCGCGTTCCG
181 GCGTCTCCTTGCGCGCCCCGGCTCCCGGCTGTCCCCGCCCGGCGTGCGAGCCGGTGTATG
241 SCA2-A
GGCCCCTCACCATGTCGCTGAAGCCCCAGCAGCAGCAGCAGCAGCAGCAGCAACAGCAGC
301 AGCAGCAACAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCCGCCGCCCGCGGCTGCCAATGTCCGCA
361 SCA2-B
AGCCCGGCGGCAGCGGCCTTCTAGCGTCGCCCGCCGCCGCGCCTTCGCCGTCCTCGTCCT
421 CGGTCTCCTCGTCCTCGGCCACGGCTCCCTCCTCGGTGGTCGCGGCGACCTCCGGCGGGCG
481 GGAGGCCCGGCCTGGGCAG GTGGGTGTCGGCACCCC

FIG. 2

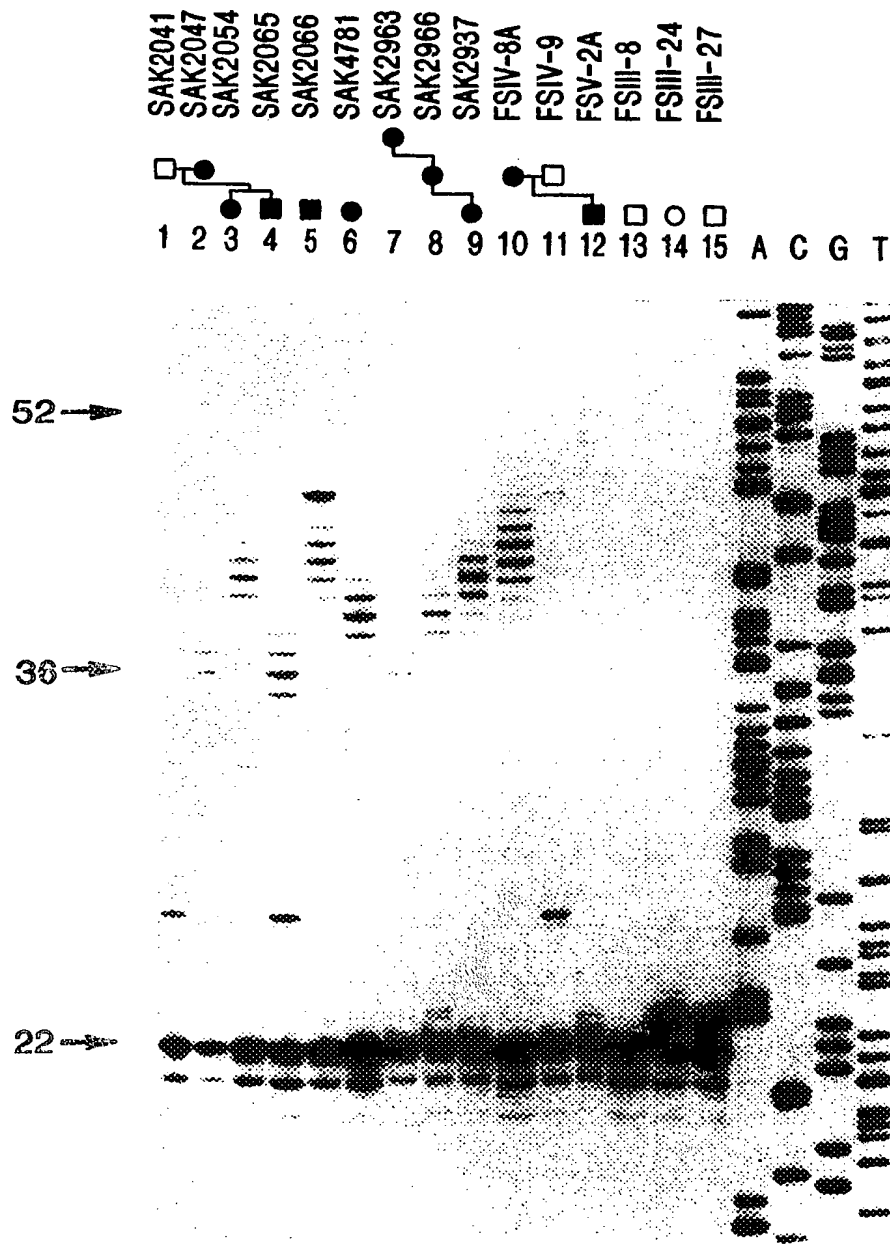


FIG. 3

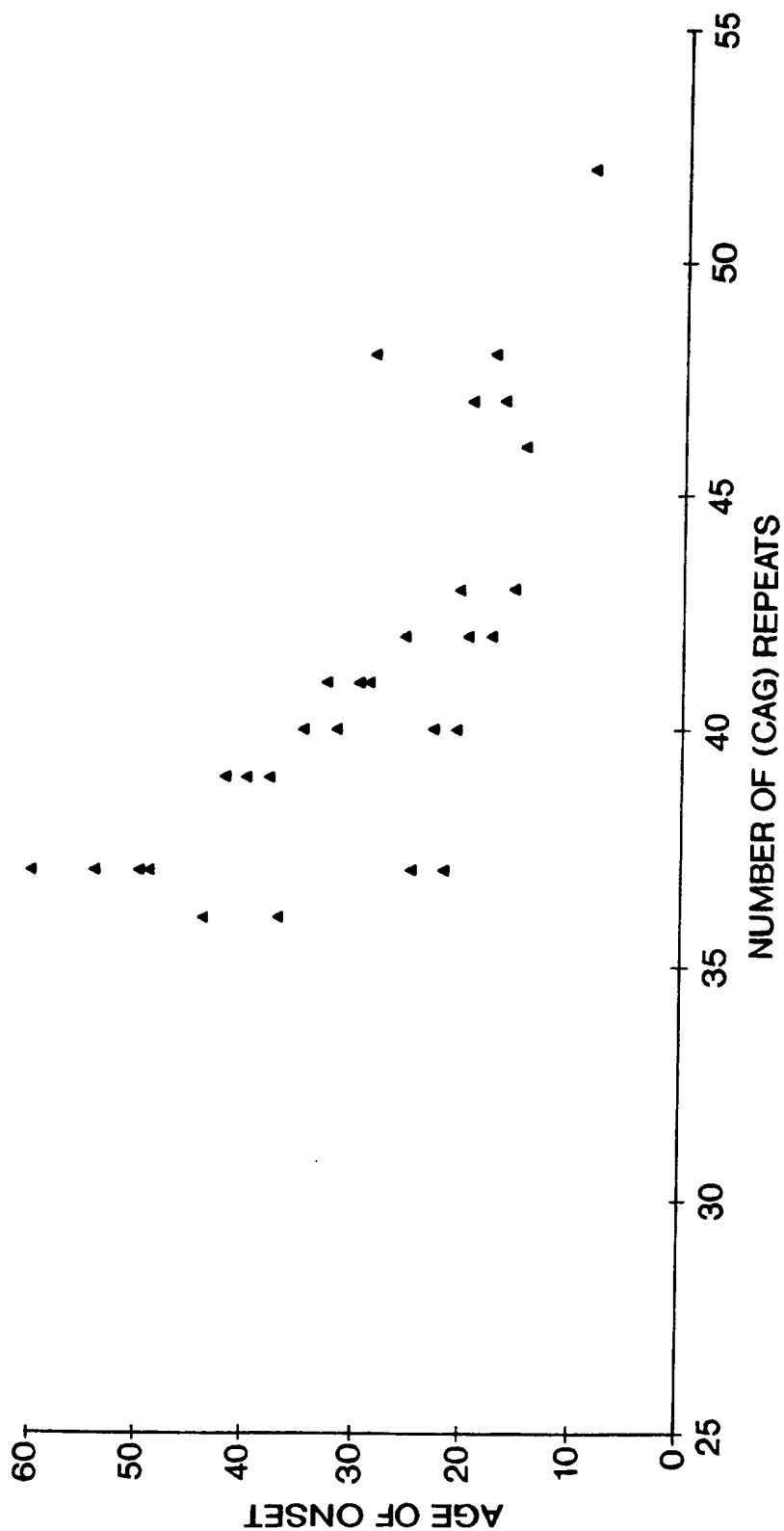


FIG. 4

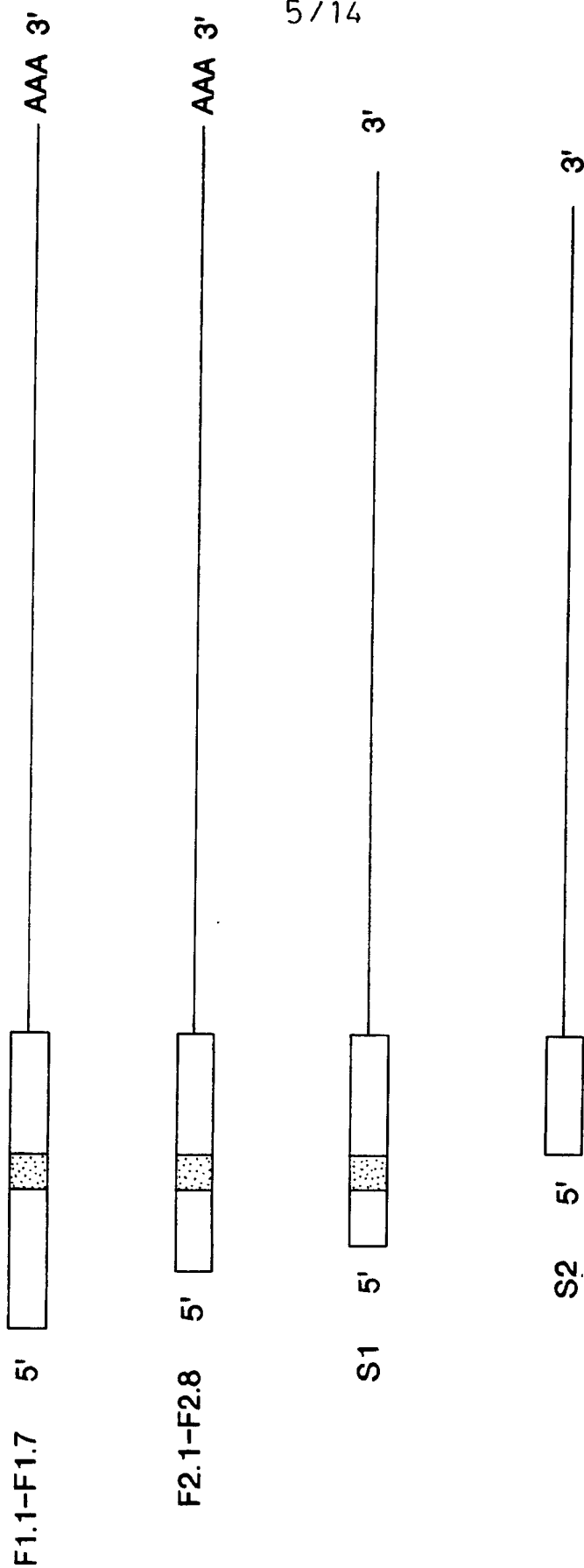


FIG. 5

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```

1  ACCCCGAGAAAGCAACCCAGCGCGCCCGCTCCTCAGTGTCCCTCCCGGCCCGGG 60
61  GCCACCTCAGGTTCTGCTTCCGTCAGACCCCTCCGACTTCCGGTAAAGAGTCCCTATCCG 120
    *
121  CACCTCCGCTCCCACCCGGCGCCTCGGCGGCCCGCCCTCCGATGCGCTCAGCGGCCGCA 180
    1      M R S A A A
181  GCTCCTCGGAGTCCCGGGTGGCCACCGAGTCTCGCCGCTTCCGCCGAGCCAGGTGGCCC 240
    7  A P R S P A V A T E S R R F A A A R W P 26
241  GGTGGCGCTCGCTCCAGCGCGCCGGCGGAGCGGGCGGCGGTGGCGCGGCC 300
    27  G W R S L Q R P A R R S G R G G G A A 46
301  CCGGACCGTATCCCTCCGCGCCCTCCCGCGCCCGCCCGCCCTCCCTCCCGG 360
    47  P G P Y P S A A P P P P G P P P S R 66
361  CAGAGCTCGCCTCCCTCCGCCCTCAGACTGTTTGGTAGCAACGGCAACGGCGCGCGG 420
    67  Q S S P P S A S D C F G S N G N G G A 86
421  TTTCCGCGCGGCTCCCGCGGCTCCTTGGTCTCGGCGGCTCCCGCCCTTCGTGTC 480
    87  F R P G S R R L L G L G G P P R P F V V 106
481  GTCCTTCTCCCTCCAGCCCGGCGCCCTCCCGCGCGCCCAACCGCGCTCCCGG 540
    107  V L L P L A S P G A P P A A P T R A S P 126
541  CTCGGCGCCCGTGCTCCCGCGGCTTCCGGCGTCTCCTTGGCGCGCCCGCTCCCGGC 600
    127  L G A R A S P P R S G V S L A R P A P G 146
    SCA2-A
601  TGTCCCGCGCGGCGTGGAGCCGGTGATGGGCCCCCTCACCATGTGCTGAAGCCCCAG 660
    147  C P R P A C E P V Y G P L T M S L K P Q 166
661  CAGCAGCAGCAGCAGCAGCAACAGCAGCAGCAACAGCAGCAGCAGCAGCAGCAG 720
    167  Q Q Q Q Q Q Q Q Q Q Q Q Q Q Q Q Q Q 186

```

FIG. 6A

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SCA2-B

721 CAGCCGCCGCCGGCTGCCAATGTCCGCAAGCCCGGCGGAGCGCCTTCTAGCGTCG 780
 187 Q P P A A A N V R K P G G S G L L A S 206
 781 CCCGCCCGCGCCTTCGCGCTCCTCGTCTCGGTCTCCTCGTCTCGGCCACGGCTCCC 840
 207 P A A P S S S S S V S S S A T A P 226
 841 TCCTCGGTGGTCGCGGACCTCCGGCGGCGGAGGCCCGCCTGGGCAGAGGTCGAAAC 900
 227 S S V V A A T S G G G R P G L G R G R N 246
 901 AGTAACAAAGGACTGCCTCAGTCTACGATTTCTTTGATGGAATCTATGCAAAATATGAGG 960
 247 S N K G L P Q S T I S F D G I Y A N M R 266
 961 ATGGTTCAATATACTTACATCAGTTGTGGCTCCAAATGTGAAGTACAAGTGAATAATGGA 1020
 267 M V H I L T S V V G S K C E V Q V K N G 286

SCA2-14B

1021 GGTATATGAAGGAGTTTAAACTTACAGTCCGAAGTGTGATTTGGTACTTGATGCC 1080
 287 G I Y E G V F K T Y S P K C D L V L D A 306
 1081 GCACATGAGAAAAGTACAGAAATCCAGTTCGGGGCCGAAACGTGAAGAAATAATGGAGAGT 1140
 307 A H E K S T E S S S G P K R E E I M E S 326
 1141 ATTTGTTCAAATGTTTCAGACTTTGTGTGTACAGTTTAAAGATATGGACTCCAGTTAT 1200
 327 I L F K C S D F V V V Q F K D M D S S Y 346
 1201 GCAAAAAGAGATGCTTTTACTGACTCTGCTATCAGTGTAAAGTGAATGGCGAACACAAA 1260
 347 A K R D A F T D S A I S A K V N G E H K 366
 1261 GAGAAGGACCTGGAGCCCTGGGATGCAGGTGAACCTCACAGCCCAATGAGGAACCTTGAGGCT 1320
 367 E K D L E P W D A G E L T A N E E L E A 386
 1321 TTGGAATAATGACGTATCTAATGGATGGATCCCAATGATATGTTTCGATATAATGAAGAA 1380
 387 L E N D V S N G W D P N D M F R Y N E E 406
 1381 AATTATGGTGTAGTGTCTACGTATGATAGCAGTTTATCTTCGTATACAGTGCCCTTAGAA 1440
 407 N Y G V V S T Y D S S L S S Y T V P L E 426
 1441 AGAGATAACTCAGAAGAATTTTAAACGGGAAGCAAGGGCAACACAGTTAGCAGAAGAA 1500
 427 R D N S E E F L K R E A R A N Q L A E E 446

FIG. 6B

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1501 ATTGAGTCAAGTGGCCAGTACAAAGCTCGAGTGGCCCTGGAAATGATGATAGGAGTGAG 1560
 447 I E S S A Q Y K A R V A L E N D D R S E 466
 1561 GAAGAAAATACACAGCAGTTCAGAGAAATTCAGTGAACGTGAGGGCACAGCATAAAC 1620
 467 E E K Y T A V Q R N S S E R E G H S I N 486
 1621 ACTAGGGAAAATAATATATTCCTCCTGGACAAAGAAATAGAGAAGTCATATCCTGGGGA 1680
 487 T R E N K Y I P P G Q R N R E V I S W G 506
 1681 AGTGGGAGACAGAATTCACCGCGTATGGGCCAGCCTGGATCGGGCTCCATGCCATCAAGA 1740
 507 S G R Q N S P R M G Q P G S G S M P S R 526
 1741 TCCACTTCTCACACTTCAGATTTCAAACCCGAATTCTGTTTCAGACCACCAAGAGTAGTTAAT 1800
 527 S T S H T S D F N P N S G S D Q R V V N 546
 1801 GGAGGTGTTCCCTGGCCATGCGCTTGCCCATCTCCTTCCTCTCGCCACCTTCTCGCTAC 1860
 547 G G V P W P S P C P S P S S R P P S R Y 566
 1861 CAGTCAGTCCCAACTCTCTTCCACCTCGGGCAGCCACCCCTACACGGCGCCCTCCAGG 1920
 567 Q S G P N S L P P R A A T P T R P P S R 586
 1921 CCCCCCTCGGGCCATCCAGACCCCCGTCTCACCCCTCTGCTCATGGTTCTCCAGCTCCT 1980
 587 P P S R P S R P P S H P S A H G S P A P 606
 1981 GTCTCTACTATGCCCTAAACGCATGTCTTCAGAAAGGCGCTCCAAGGATGTCCCCCAAAGGCC 2040
 607 V S T M P K R M S S E G P P R M S P K A 626
 2041 CAGCGACATCCTCGAAATCACAGAGTTTCTGCTGGAGGGGTTCCATATCCAGTGGCCTA 2100
 627 Q R H P R N H R V S A G R G S I S S G L 646
 2101 GAATTTGTATCCCAACCAACCCAGTGAAGCAGCTACTCCTCCAGTAGCAAGGACCAGT 2160
 647 E F V S H N P P S E A A T P P V A R T S 666
 2161 CCCTCGGGGAACGTGGTCATCAGTGGTCAGTGGGTTCCAAGATTATCCCCTAAACT 2220
 667 P S G G T W S S V V S G V P R L S P K T 686
 2221 CATAGACCCAGGTCTCCAGACAGACAGTATTGGAAATACCCCCAGTGGGCCAGTTCTT 2280
 687 H R P R S P R Q N S I G N T P S G P V L 706

FIG. 6C

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2281	GCTTCTCCCCAAGCTGGTATTATTCCAACTGAAGCTGTTGCCATGCCTATTCAGCTGCA	2340
707	A S P Q A G I I P T E A V A M P I P A A	726
2341	TCTCCTAGCCTGCTAGTCTGCTGATCGAACAGAGCTGTTACCCCTTCTAGTGAGGCTAAA	2400
727	S P T P A S P A S N R A V T P S S E A K	746
2401	GATTCCAGGCTTCAAGATCAGAGGCAGAACTCTCCTGCAGGGAATAAAGAAAATATTAAA	2460
747	D S R L Q D Q R Q N S P A G N K E N I K	766
2461	CCCAATGAACATCACCTAGCTTCTCAAAAGCTGAAACAAAGGTATATCACCAAGTTGT	2520
767	P N E T S P S F S K A E N K G I S P V V	786
2521	TCTGAACATAGAAAACAGATTGATGATTTAAGAAATTTAAGAATGATTTTAGGTTACAG	2580
787	S E H R K Q I D D L K K F K N D F R L Q	806
2581	CCAAGTTCTACTTCTGAATCTATGGATCAACTACTAAACAAAATAAGAGGGAGAAAAA	2640
807	P S S T S E S M D Q L L N K N R E G E K	826
2641	TCAAGAGATTTGATCAAGACAAAATTGAACCAAGTGCTAAGGATTCCTTCATTGAAAAT	2700
827	S R D L I K D K I E P S A K D S F I E N	846
2701	AGCAGCAGCAACTGTACCAGTGGCAGCAGCAAGCCGAATAGCCCCAGCATTTCCCTTCA	2760
847	S S S N C T S G S S K P N S P S I S P S	866
2761	ATACTTAGTAACAGGAGCACAAAGAGGGACCTGAGTCACTTCCCAAGGGTTTCAGACT	2820
867	I L S N T E H K R G P E V T S Q G V Q T	886
2821	TCCAGCCCAGCATGTAAACAGAGAAAGACGATAAGGAAGAGAAAGACGAGCTGAG	2880
887	S S P A C K Q E K D D K E E K K D A A E	906
2881	CAAGTAGGAAATCAACATTGAATCCCAATGCCAAAGGAGTTCAACCCACGTTCTCTCT	2940
907	Q V R K S T L N P N A K E F N P R S F S	926
2941	CAGCCAAAGCCTTCTACTACCCCACTTCACCTCGGCCTCAAGCACAACTAGCCCATCT	3000
927	Q P K P S T T P T S P R P Q A Q P S P S	946
3001	ATGGTGGTTCATCAACAGCCAACTCCAGTTTATACTCAGCCTGTTTGTTCACCAAT	3060
947	M V G H Q Q P T P V Y T Q P V C F A P N	966
3061	ATGATGTATCCAGTCCAGTGAGCCCGGCGTGCAACCTTTATACCCCAATACCTATGACG	3120
967	M M Y P P V P V S P G V Q P L Y P I P M T	986

FIG. 6D

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3121	CCCATGCCAGTGAATCAAGCCCAAGACATATAGAGCAGTACCAATAATGCCCCAACAGCGG	3180
987	P M P V N Q A K T Y R A V P N M P Q Q R	1006
3181	CAAGACCAGCATCATCAGAGTGCCATGATGCACCCAGCGTCAGCAGCGGGCCCCACCGATT	3240
1007	Q D Q H H Q S A M M H P A S A A G P P I	1026
3241	GCAGCCACCCACAGCTTACTCCACGCAATATGTTGCCCTACAGTCCTCAGCAGTTCCCA	3300
1027	A A T P P A Y S T Q Y V A Y S P Q Q F P	1046
3301	AATCAGCCCCCTTGTTTCAGCATGTGCCACATTATCAGTCTCAGCATCCTCATGTCTATAGT	3360
1047	N Q P L V Q H V P H Y Q S Q H P H V Y S	1066
3361	CCTGTAATACAGGGTAATGCTAGAAATGATGGCACCCACCAACACACGCCCTGGTTTA	3420
1067	P V I Q G N A R M M A P P T H A Q P G L	1086
3421	GTATCTTCTTCAGCAACTCAGTACGGGCTCATGAGCAGACGCATGCGATGTATGCATGT	3480
1087	V S S A T Q Y G A H E Q T H A M Y A C	1106
3481	CCCAAATTACCATAACAAGGAGACAAAGCCCTTCTTTCTACTTTTGCCATTTCACGGGC	3540
1107	P K L P Y N K E T S P S F Y F A I S T G	1126
3541	TCCCTTGCTCAGCAGTATGGCACCCCTAACGCTACCTGCACCCACATACTCCACACCCCT	3600
1127	S L A Q Q Y A H P N A T L H P H T P H P	1146
3601	CAGCCTTCAGCTACCCCACTGGACAGCAGCAAGCCCAACATGGTGGAAGTCATCCTGCA	3660
1147	Q P S A T P T G Q Q Q S Q H G G S H P A	1166
3661	CCCAGTCCTGTTTCAGCACCATCAGCACCCAGGCGGCCAGGCTCTCCATCTGGCCAGTCCA	3720

FIG. 6E

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1167 P S P V Q H H Q H Q A A Q A L H L A S P 1186
3721 CAGCAGAGTCAGCCATTATACCACGGGGGCTTGGCCCACTCCACCCTCCATGACACCT 3780
1187 Q Q Q S A I Y H A G L A P T P P S M T P 1206
3781 GCCTCCAAACACGCAGTCGCCACAGAAATAGTTTCCAGCAGCACAAACAGACTGCTTTACG 3840
1207 A S N T Q Q S P Q N S F P A A Q Q T V F T 1226
3841 ATCCATCCTTCTCAGCTTCAGCCGGGTATACCAACCCACCCACATGGCCCACGTACCT 3900
1227 I H P S H V Q P A Y T N P P H M A H V P 1246
3901 CAGGCTCATGTACAGTCAGGAATGGTTCTTCTCATCCAACTGCCCATGGCCCAATGATG 3960
1247 Q A H V Q S G M V P S H P T A H A P M M 1266
3961 CTAATGACGACACAGCCACCCGGCGGTCCCCAGGCCGCCCTCGCTCAAAGTGCACATACAG 4020
1267 L M T T Q P P G G P Q A A L A Q S A L Q 1286
4021 CCCATTCCAGTCTCGACAAACAGCGCATTTCCCTATATGACGCACCCTTCAGTACAAGCC 4080
1287 P I P V S T T A H F P Y M T H P S V Q A 1306
4081 CACCACCAACAGCAGTTGTAGGCTGCCCTGGAGGAACCGAAAGGCCAAATTCCCTCCTC 4140
1307 H H Q Q Q L * 1326
4141 CCTTCTACTGCTTCTACCAACTGGAAGCACAGAAAAGTAAATTTTATTTGTTTT 4200
4201 TAAATATATATGTTGATTCTTGTAAACATCCAATAGGAATGCTAACAGTTCACTTGCAG 4260
4261 TGGAGATACCTTGGACCGAGTAGAGGCATTTAGGAACCTTGGGGGTATTCATAATCCA 4320
4321 TATGCTGTTTCAGAGTCCCGCAGGTACCCAGCTCTGCTTGCCGAAACTGGAAGTTATTT 4380
4381 ATTTTAAATACCCCTTGAAAGTCATGAACACATCAGCTAGCAAAAGAAAGTAAACAAGT 4440
4441 GATTCTTGCTGCTATTACTGCTAAAAAATAAAAAA 4481

FIG. 6F

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Ataxin-2	1	VYGPLTMSLK	PQQQQQQQQQ	QQQQQQQQQQ	QQQPPAAAN	VRKPGGSGLL	50
Mouse Ataxin-2		HEGPLTMSLK	PQPQPPAPAT	GRKPGG.GLL	
A2RP	LA	PQPPPPQHQ	ER	
Consensus		-----L-	PQ-----	-----	-----	-----	
Ataxin-2	51	ASPAAAPSPS	SSSVSSSSAT	APSSVVA...	ATSGGGRPGL	GRGRNSNKGL	100
Mouse Ataxin-2		SSPGAAP.AS	AAVTSASVVP	APAAPVASSS	AAAGGGRPGL	GRGRNSNKGL	
A2RP		..PGAAAIGS	A.....RQSTGKGP	
Consensus		--P-AA---	S-----	-----	-----	-RG----	KG-
Ataxin-2	101	PQSTISFDGI	YANMRMVHIL	TSVVGSKCEV	QVKNGGIYEG	VFKTYSPKCD	150
Mouse Ataxin-2		PQPTISFDGI	YANVRMVHIL	TSVVGSKCEV	QVKNGGIYEG	VFKTYSPKCD	
A2RP		PQSPV.FEGV	YNNSRMLHFL	TAVVGSTCDV	KVKNGTTYEG	IFKTLSSKFE	
Consensus		PQ----F-G-	Y-N-RM-H-L	T-VVGS-C-V	-VKNG--YEG	-FKT-S-K--	
Ataxin-2	151	LVLDAAHEKS	TESSSGPKRE	EIMESILFKC	SDFVVVQFKD	MDSSYAKRDA	200
Mouse Ataxin-2		LVLDAAHEKS	TESSSGPKRE	EIMESVLFKC	SDFVVVQFKD	TDSSYARRDA	
A2RP		LAVDAVHRKA	SEPAGGPRRE	DIVDTMVFKP	SDVMLVHFRN	VDFNYATKDK	
Consensus		L--DA-H-K-	-E---GP-RE	-I-----FK-	SD---V-F--	-D--YA--D-	

FIG. 7A

Ataxin-2	201	FTDSAIS..A	KVNGEHKEKD	LEPWDAGELT	ANEELALEN	DVSNGWDPND	250
Mouse Ataxin-2		FTDSALS..A	KVNGEHKEKD	LEPWDAGELT	ASEELE.LEN	DVSNGWDPND	
A2RP		FTDSAIAMNS	KVNGEHKEKV	LQRWEGGD.S	NSDDYD.LES	DMSNGWDPNE	
Consensus		FTDSA-----	KVNGEHKEK-	L--W--G----	-----LE-	D-SNGWDPN-	
Ataxin-2	251	MFRYNEENYG	VVSTYDSSL	SYTVPLERDN	SEEFLEKREAR	ANQLAEEIES	300
Mouse Ataxin-2		MFRYNEENYG	VVSTYDSSL	SYTVPLERDN	SEEFLEKREAR	ANQLAEEIES	
A2RP		MFKFNEENYG	VKTTYDSSL	SYTVPLEKDN	SEEFQRQREL	AAQLAREIES	
Consensus		MF--NEENYG	V--TYDSSL	SYTVPLE-DN	SEEF--RE-R	A-QLA-EIES	
Ataxin-2	301	SAQYKARVAL	ENDD.RSEEE	KYTAVQRNCS	EREGHSINTR	ENKYIPPGQR	350
Mouse Ataxin-2		SAQYKARVAL	ENDD.RSEEE	KYTAVQRNCS	DREGHGPNT	DNKYIPPGQR	
A2RP		SPQYRLRIAM	ENDDGRTEEE	KHSAVQRQGS	GRESPLASR	EGKYIP....	
Consensus		S-QY--R-A-	ENDD-R-EEE	K--AVQR--S	-RE-----R	--KYIP----	
Ataxin-2	351	NR					
Mouse Ataxin-2		NR					
A2RP		..					
Consensus		--					

FIG. 7B

SCA2 Gene

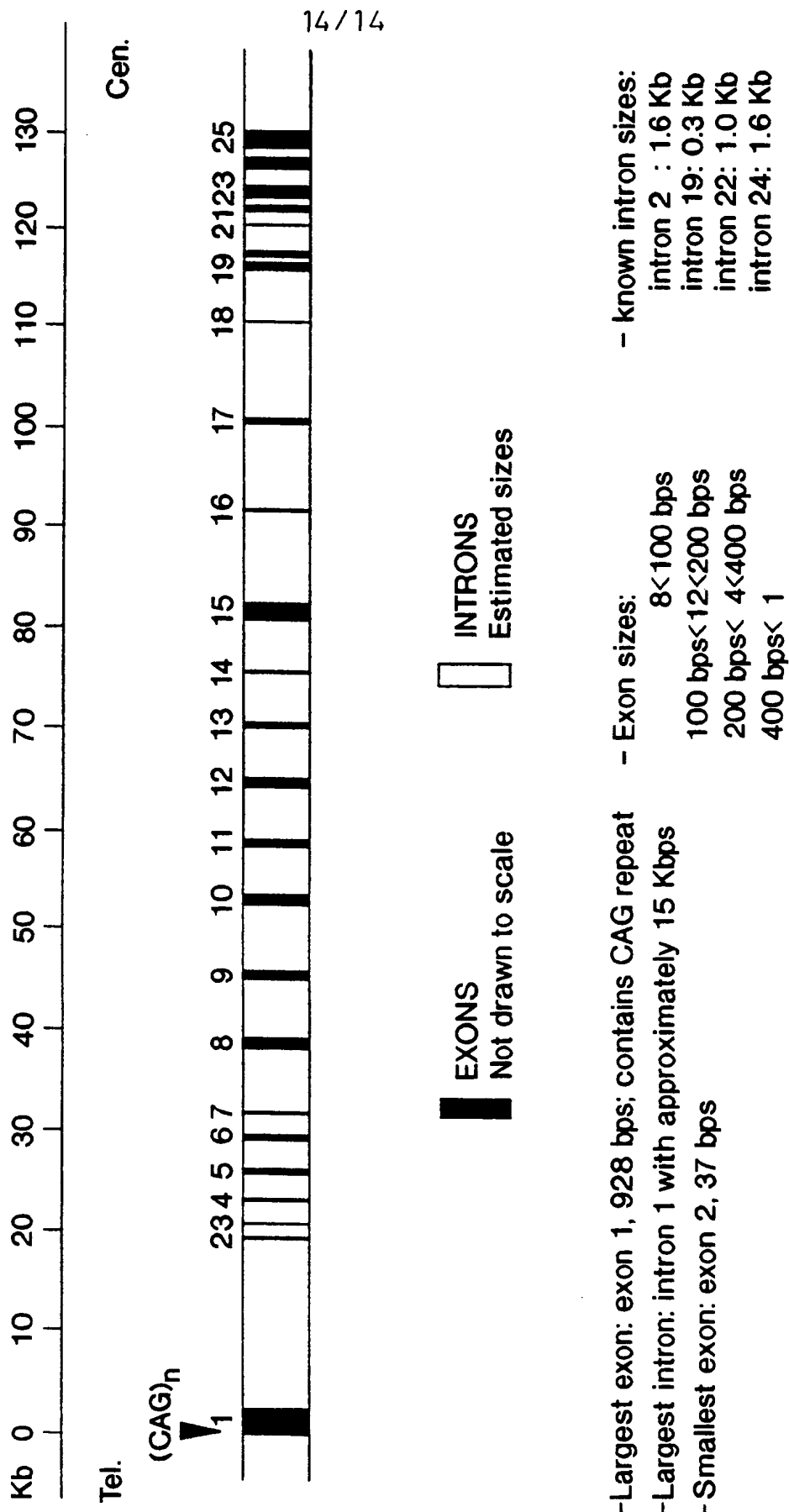


FIG. 8

INTERNATIONAL SEARCH REPORT

Internat Application No

PCT/US 97/07725

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C12N15/00 C12N15/12 C12N5/10 C07K14/47 C07K16/18
 C12Q1/68 G01N33/577 A01K67/027

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C12N C07K C12Q G01N A01K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
E	WO 97 17445 A (CENTRE NAT RECH SCIENT ;INST NAT SANTE RECH MED (FR); TORA LAZSLO) 15 May 1997 see page 18, line 25 - page 21, line 14 ---	1-30, 37-43
X	NATURE, vol. 378, no. 6555, 23 November 1995, pages 403-406, XP002009617 TROTIER Y ET AL: "POLYGLUTAMINE EXPANSION AS A PATHOLOGICAL EPITOPE IN HUNTINGTON'S DISEASE AND FOUR DOMINANT CEREBELLAR ATAXIAS" see the whole document --- -/-	24,25,39

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

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 "&" document member of the same patent family

Date of the actual completion of the international search

28 August 1997

Date of mailing of the international search report

16.09.97

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Hornig, H

INTERNATIONAL SEARCH REPORT

Inter. Int. Application No.

PCT/US 97/07725

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A	WO 95 01437 A (UNIV MINNESOTA) 12 January 1995 see the whole document ---	1-43
P,X	HUMAN MOLECULAR GENETICS, vol. 5, no. 12, December 1996, pages 1887-1892, XP002027564 STEVANIN G ET AL: "SCREENING FOR PROTEINS WITH POLYGLUTAMINE EXPANSIONS IN AUTOSOMAL DOMINANT CEREBELLAR ATAXIAS" see the whole document ---	24,25,39
P,X	NATURE GENETICS, vol. 14, no. 3, November 1996, NATURE PUBLISHING CO., NEW YORK, US, pages 269-276, XP002039149 S.-M. PULST ET AL.: "Moderate expansion of a normally biallelic trinucleotide repeat in spinocerebellar ataxia type 2" see the whole document ---	1-23,37, 40
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International Application No

PCT/US 97/07725

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